THE PREPARATION OF PYRIDINE DICARBOXYLIC ACIDS BY OZONE OXIDATION

and

THE PREPARATION OF FLUORINE-CONTAINING MEDICINALS

by

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The author wishes to express sincerest gratitude to Dr. Calvin A. VanderWerf for his guidance, assistance and encouragement during the course of these investigations.

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PART I

THE PREPARATION OF PYRIDINE DICARBOXYLIC ACIDS BY OZONE OXIDATION

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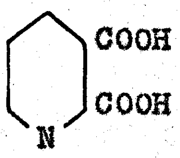
THE PREPARATION OF PYRIDINE DICARBOXYLIC ACIDS BY OZONE OXIDATION

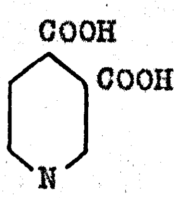
INTRODUCTION

Aromatic dicarboxylic acids have recently gained an important place as synthetic intermediates in the preparation of medicinals. A similar group of important compounds which have not been thoroughly investigated as synthetic intermediates are the pyridine dicarboxylic acids. This is due in part to the difficulty of obtaining suitable quantities of these acids by convenient methods.

In an attempt to develop a convenient synthesis for quinolinic acid (I) (pyridine-2, 3-dicarboxylic acid) and cinchomeronic acid (II) (pyridine-3,4-dicarboxylic acid), a study was made of the ozone oxidation of quinoline, 8-hydroxyquinoline and isoquinoline. Mainly out of theoretical interest,



I



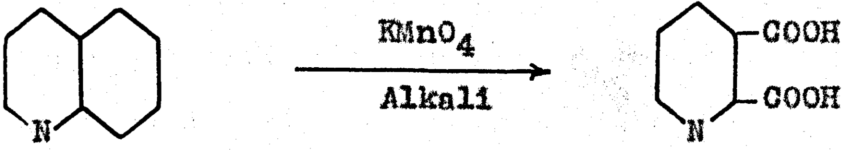
II

the investigation was extended to include 6-aminoquinoline, 6-nitroquinoline, 6-fluoroquinoline, and 6-fluoro-8-aminoquinoline.

The manufacture of pyridine dicarboxylic acids by the action of ozone on quinoline and its derivatives has been previously claimed by Ennis[1] in a British patent in 1914. However, the patent completely fails to report any details concerning the ozonization procedure, the isolation and characterization processes, and the yields. No other references regarding the action of ozone on these compounds appear in the literature.

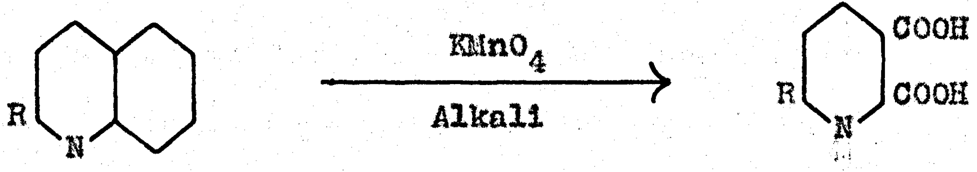
A. Preparation of Pyridine Dicarboxylic Acids:

Quinolinic acid was first synthesized in 1879 by the alkaline oxidation of quinoline with potassium permanganate.[2,3,4,5,6,7.] Proceeding on the principle

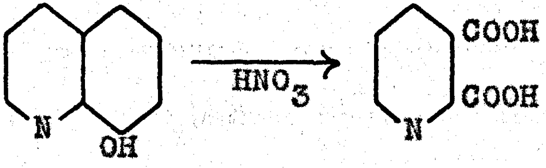


that the pyridine nucleus is more resistant to oxidation than the benzene nucleus, quinoline obtained from coal tar was oxidized by the heating of an alkaline solution with potassium permanganate. Removal of the insoluble manganese dioxide by filtration and acidification of the remaining solution gave quinolinic acid in low yields.[3]

A significant difference in the pyridine nucleus and the benzene nucleus of quinoline is that substitution affects the benzene nucleus exclusively, whereas various substituted groups can be introduced into the pyridine nucleus only by indirect methods, for instance, during synthesis. This difference is of interest because such substituents as hydroxyl[8,9,10,11], methyl[4], and sulfonic[8] groups in the benzene nucleus facilitate its oxidation. Substituted groups in the pyridine nucleus, however, show no effect on the rate of oxidation of the benzene nucleus and remain unoxidized in the pyridine nucleus, thus permitting the synthesis of numerous substituted quinolinic acid derivatives.



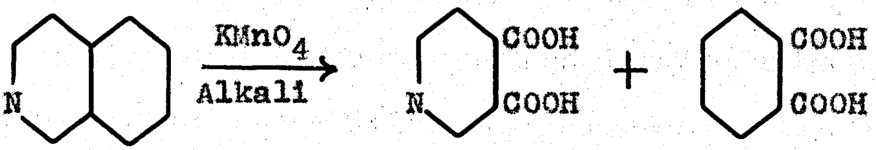
Utilizing the principle that the oxidation of the benzene nucleus is facilitated by the presence of substituted groups, Sucharda[12] synthesized quinolinic acid by the oxidation of 8-hydroxyquinoline with nitric acid. The oxidation was carried out slowly by the dropwise addition of nitric acid to quinoline over a twenty-four hour period. The solution was partially evaporated and the quinolinic acid which separated from solution was further purified by recrystallization. The quinolinic acid thus obtained is usually in the form of a nitrate, and hydrolysis and further purification are necessary in order to obtain the pure product.



The foregoing methods for the preparation of quinolinic acid by the oxidation of quinoline or substituted quinolines with alkaline permanganate or nitric acid[13,14,15,16,17] are, according to Stiks and Bulgach[18], unsatisfactory for the continuous preparation of large quantities of quinolinic acid. A more feasible method is offered by the oxidation of quinoline with hydrogen peroxide in the presence of copper sulfate. Hydrogen peroxide alone does not appreciably attack quinoline, but in the presence of copper sulfate and sulfuric acid, an insoluble quinolinic copper salt separates from the solution in 70% yields. The addition or presence of ferrous sulfate, however, not only results in an appreciable attack on the benzene nucleus, but also on the pyridine nucleus, splitting off the nitrogen with the evolution of ammonia. It is thought that in both cases the oxidation first disrupts the benzene nucleus, but that in the case of the copper sulfate the oxidation is much faster, and the quinolinic acid primarily formed does not form an insoluble iron salt. Therefore, the quinolinic acid is not removed from the field of oxidation, and splitting of the pyridine nucleus with the elimination of ammonia follows. Thus, minute quantities of iron present in the reacting solution tend to reduce the yield. The limiting value below which the iron content appears to have little effect is 0.04%, but the presence of 0.2% of iron cuts the yield from 70% to 30%.

Quinoline may also be oxidized electrically[19,20,21,22] at a platinum anode in 75% sulfuric acid, to give a yield of 77% quinolinic acid. The quinolinic acid is separated from the anolyte by washing with 30% sodium hydroxide until just acid to Congo red, followed by the formation of the copper salt and the regeneration of the quinolinic acid by treatment with hydrogen sulfide.

Cinchomeronic acid (pyridine-3,4-dicarboxylic acid) is considerably more difficult to obtain than quinolinic acid. It is prepared mainly by the oxidation of quinine hydrochloride with nitric acid.[23,24,25,26]. It can also be prepared, like quinolinic acid, by the alkaline oxidation of isoquinoline with potassium permanganate.[27,28].



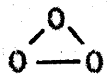
The pyridine nucleus in isoquinoline, however, is not as stable as that in quinoline, and oxidation attacks both the benzene nucleus and the pyridine nucleus simultaneously, producing cinchomeronic acid and phthalic acid. Substitution of various radicals in the benzene nucleus facilitates the oxidation but apparently does not prevent the oxidation of the pyridine nucleus.

Cinchomeronic acid has also been prepared by the oxidation of 3,4-dimethyl pyridine[29] in small yields, but the extreme difficulty of obtaining 3,4-dimethyl pyridine makes this method impractical.

B. Ozonization Reaction:

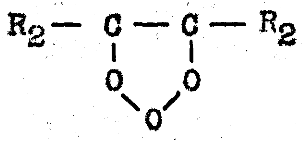
The theoretical treatment of ozonolysis has been applied successfully to many questions of structure, but until recently its utilization as a means of synthesis has not been extensively developed. The slow development of the utilization of ozonolysis for the synthesis of organic compounds can be readily understood when one considers the various factors which govern the reaction. Such factors as the ozone concentration, the duration and rate of ozonization, the temperature of the reaction, the solvent, the concentration of the solution, and, most important of all, the decomposition of unstable or highly stable ozonides, are all sensitive and important factors.

In formulating a theory of ozonolysis, consideration must first be given to the structure of the ozone molecule. Many arrangements of the oxygen atoms have been presented, of which the two most commonly considered are:[30]

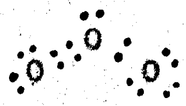


$O=O=O$

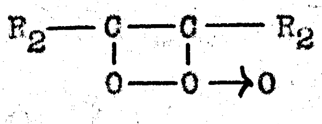
The structure assigned to the corresponding ozonide, assuming either of the latter structures for ozone, is:



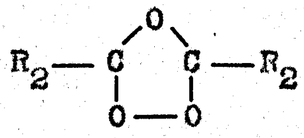
However, upon reduction, such a structure yields glycols and not aldehydes and ketones, as obtained experimentally. The pronounced reactivity of one of the three oxygen atoms in the ozone molecule is not accounted for by either of these structures, and a third formula, in which two oxygen atoms are linked by a double bond, and the third by a coordinate covalent bond, is currently accepted.[31]



The ozone molecule is not a linear molecule, but physical measurements indicate the angle between the oxygen atoms to be 127°. The structure assigned to the corresponding primary ozonide is:



This is then believed to change, sometimes with explosive violence, into an iso-ozonide, which appears to be the stable form:



It has been found necessary to vary the concentration of ozone bubbled through a solution to be ozonized in accordance with the nature of the compound being treated. A high concentration of ozone (14-15%), facilitates addition of the reagent to aromatic compounds and substances with conjugated double bonds[32], whereas a low concentration (1-5%), is essential for the isolation of certain aldehydes which are sensitive to oxidation. The concentration of the ozone may be reduced by passing the gas through a solution of sodium hydroxide before entering the ozonization vessel. In almost every instance, excessive ozonization must be avoided, because of the oxidative effect of the excess ozone on the reaction products. When complete absorption of ozone does not occur, this factor becomes one of the most difficult problems in the reaction.

A number of solvents have been found useful, and no general rule can be stated for the proper selection of a solvent. Although substances which are attacked by ozone would seem inapplicable, this is not necessarily the case, for methyl alcohol, chloroform, and other liquids known to be sensitive to ozone have been used successfully. Dry, pure, ethyl acetate, according to Fisher[33], is the best solvent for a number of alicyclic and aliphatic unsaturated compounds. Acetic acid, hexane, petroleum ether, carbon tetrachloride, and methyl and ethyl chlorides have been used successfully.

The concentration of the solution may be varied widely but for most olefins, dilute solutions and low temperatures are preferred[33]. For aromatic substances, in cases where the material is liquid, no solvent is necessary, but the danger of explosion in such cases is greatly increased.

The relative rates of ozonization of different compounds have been studied. Compounds containing two conjugated double bonds were found to add the first mole of ozone more rapidly than the second[30]. Brus and Peyresblanques[34] ozonized styrene, phenylcyclohexene, benzene, and heptyne, and found that, with a 9 to 10% concentration of ozone, benzene added ozone extremely slowly, and heptyne moderately so. The other compounds added one mole of ozone very rapidly.

Noller[35] ozonated a number of compounds, plotting the unabsorbed ozone against the equivalents of ozone entering the solution. From his data, he drew the following conclusions: A double bond unaffected by the presence of other groups added ozone extremely rapidly, but the rate was markedly decreased when the double bond was conjugated with carbonyl groups. Three or more phenyl groups or two chlorine atoms attached to the double bond carbons also decreased the rate of addition.

Where two or three double bonds were conjugated with each other, one bond added ozone rapidly while the others added it only slowly. In the case of cis-trans isomers where the rate of addition was decreased by other groups, the trans-isomer added ozone more rapidly than the cis-form[36]. Ozone also reacted more readily with a carbon-to-carbon double bond than with a nitrogen-to-carbon double bond.

C. Decomposition of Ozonides:

The significance of the ozonization method for the proof of structure and preparative purposes is diminished in many instances because of the unsatisfactory decomposition of the ozonide. In general, the ozonides of the higher aliphatic, simple, unsaturated hydrocarbons are very stable, like those of hydroaromatic substances. On the other hand, the ozonides of the doubly unsaturated, aliphatic hydrocarbons decompose readily. Aliphatic ozonides containing oxygen in other parts of the molecule react readily, in almost every case, with ice water. Of the various ring systems, the ozonides of six and seven-membered ring compounds are stable in comparison with those of five-membered ring compounds, while the ozonides of very high molecular weight compounds, like rubber, resinify when heated with water.

Various methods of decomposing the ozonides have been investigated and developed. Useful applications are: Decomposition with water, oxidative cleavage of the ozonides with various oxidants, decomposition with reducing agents, and catalytic hydrogenation. Straus[37] decomposed various ozonides by drawing a stream of moist air through the ozonized solution and then adding water and heating.

Oxidative cleavage of ozonides leads to acids as the products of ozonization[38]. Such oxidants as chromic acid, potassium permanganate, hydrogen peroxide, and nitric acid have been successfully used; alkaline permanganate and hydrogen peroxide are perhaps the most useful. Henne and Hill[39] obtained excellent yields of acids by decomposing the ozonides with 30% hydrogen peroxide in an acetic acid solution.

A useful and more appropriate method of decomposing ozonides and obtaining aldehydes and ketones as the products, is the use of certain reducing agents, usually immediately after the initial ozonization. Various reducing agents which have been used successfully are: Aluminum amalgam and water; zinc dust; glacial acetic acid and heat; sodium bisulfite; potassium ferrocyanide; and a mixture of zinc dust, silver nitrate, hydroquinone and water. The effectiveness of these catalysts is limited by the fact that often the ozonides must be removed from their solvents before reduction, and the isolation of the ozonide is a delicate and often impossible procedure.

Church and Whitmore[41,42] found that, of the various reduction methods for decomposing an ozonide, the use of zinc dust, water, and traces of silver nitrate (0.001 mole) and hydroquinone (0.001 mole) was by far the best. The silver nitrate destroyed the hydrogen peroxide which is formed, while the hydroquinone was added as an antioxidant catalyst, to retard the oxidation of the aldehydes to acids. Yields as high as 40% of various aldehydes, and 65% of certain ketones were obtained. The decomposition of ozonides in the presence of hydrazine was also studied in the hope that the aldehyde or ketone would immediately form a hydrazone as rapidly as it was produced, thus increasing the yield. In every case, however, the hydrazine was recovered practically quantitatively.

The use of non-aqueous media such as acetic anhydride, propionic anhydride, and liquid ammonia for the decomposition of the ozonide has been accomplished but none of these methods are promising for the quantitative determination of the products, especially the aldehydes.

A widely accepted method of decomposition, which gives good yields and is less hazardous, was developed by Fischer[44]. It involves catalytic hydrogenation of the ozonide in the presence of such catalysts as platinum-charcoal, palladium, platinic oxide, and Raney nickel. Certain precautions which have been found to increase the yields are: Ozonization at low temperatures in dilute solutions, careful avoidance of excess ozonization and hydrogenation at low temperatures. The hydrogenation usually proceeds very quickly with evolution of heat. The resultant secondary reaction, an acid rearrangement of the ozonide, increases with the temperature and was found to be the main cause for low yields of aldehydes and ketones[45]. The formation of acids becomes negligible, however, if warming is prevented during the hydrogenation. Decomposition is also facilitated by the proper selection of a solvent in which the ozonide can be hydrogenated. Halogenated solvents are relatively poor and must be removed prior to hydrogenation, whereas glacial acetic acid and ethyl acetate have been successfully used.

II. EXTENT OF PRESENT INVESTIGATION

The present investigation was based upon an attempt to develop a convenient method, resulting in good yields, for the synthesis of quinolinic and cinchomeronic acids. Known methods of obtaining these acids, as previously described, are inconvenient and often result in low yields.

The preparation of pyridine dicarboxylic acids by ozone oxidation of quinoline and isoquinoline has been mentioned in the patent literature, but details concerning the ozonolysis, isolation, and characterization procedure are lacking and therefore a thorough investigation of this promising method was undertaken.

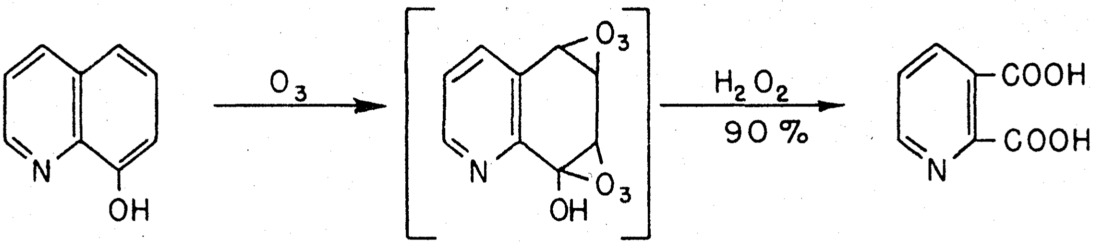
The extent of our investigation includes the study of the ozonization of quinoline, isoquinoline, and 8-hydroxyquinoline in regard to ozonization conditions, such as selective solvents, temperature, rate of addition of the first and second mole of ozone to form a mono or diozonide, and the subsequent cleavage of the ozonides by water or by oxidative or reductive methods, including catalytic hydrogenation.

Out of theoretical interest the investigation was extended to include the synthesis and ozonization of various amino, nitro, and fluoro substituted quinolines. The effect of these various electron-donating and withdrawing groups on the rate of ozonization, the stability of the resulting ozonide, and the selective attack of ozone on the nucleus of higher electron density were also determined.

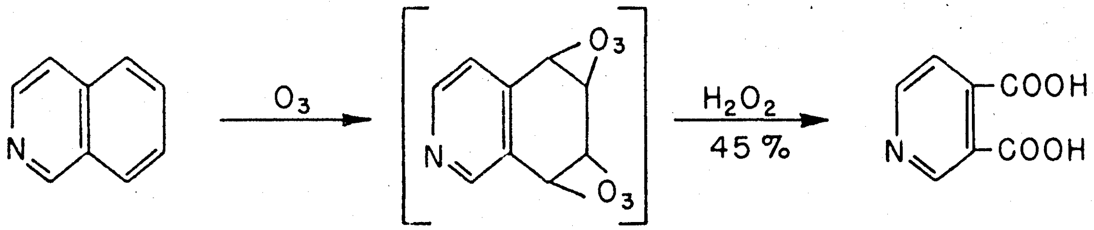
EXPERIMENTAL

I- Ozonization of 8-Hydroxyquinoline, Isoquinoline and Quinoline

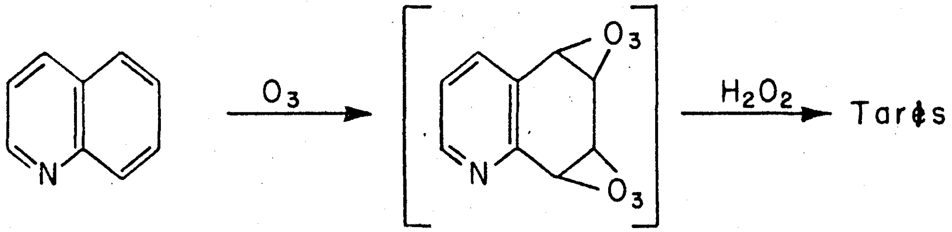
8-Hydroxyquinoline:



Isoquinoline:

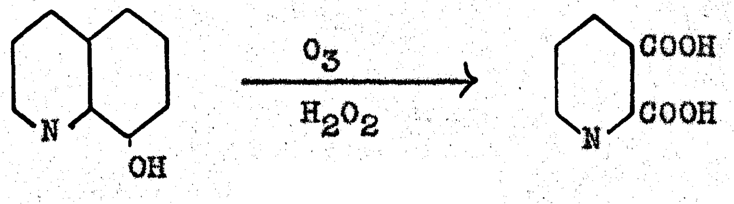


Quinoline:



III. EXPERIMENTAL

A. Ozonization of 8-Hydroxyquinoline:



145 g. (1 mole)	167.1 g. (1 mole)
145 g. (1 mole)	155 g. (0.93 mole)

$$\% \text{ Yield} = \frac{0.93}{1.00} = 93\%$$

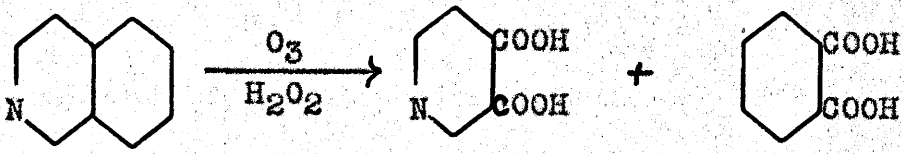
In a cylindrical ozonization flask having a capacity of 1.5 l. and designed for good dispersion of the oxonized oxygen, were placed 145 g. (1.0 mole) of 8-hydroxyquinoline and 1 l. of glacial acetic acid. The flask, surrounded by a water bath maintained at room temperature, was assembled in the ozonization apparatus and subjected to a stream of 3-4% ozonized oxygen at 40 l. per hour. During the early stages of the ozonization, the solution turned dark brown in color, and a slight rise in temperature was noted. As ozone was absorbed, the solution gradually turned yellow. The ozone was absorbed almost quantitatively until slightly less than one mole had been added; the second mole added somewhat less rapidly, as shown by the plot of the titration of the effluent gases on page 48. The ozonization was continued until no further ozone was absorbed, which requires about 90 hours under these particular conditions.

The entire ozonized solution was placed in a 3 l. flask fitted with a condenser, a stirrer, and a dropping funnel. The flask was warmed on a steam bath, and 226 g. (2.0 moles) of 30% hydrogen peroxide was added dropwise, with stirring. The mixture was then heated on the steam bath for three hours, with stirring. Any solids present were filtered; the remaining solution was concentrated under vacuum to approximately 200 ml. and then evaporated to dryness in a large evaporating dish.

The resulting yellow solid material was thoroughly washed with 100 ml. of ice-cold water and filtered on a fretted glass funnel. This procedure was repeated three times. The three washings were combined, the water removed by evaporation, and the remaining viscous material (about 20 g.) refluxed with 40 g. of 30% hydrogen peroxide for three hours. The resulting solution was treated as described above, and the crystalline solids added to those previously obtained.

After drying at 50° C. in a vacuum oven, the quinolinic acid obtained decomposed at 188-190° C. into a black solid (nicotinic acid), which remelts at 228-30° C. It was sufficiently pure for most purposes, but could be recrystallized from water if a very pure product was desired. The yield was 155 g. (93%).

B. Ozonization of Isoquinoline[47]:



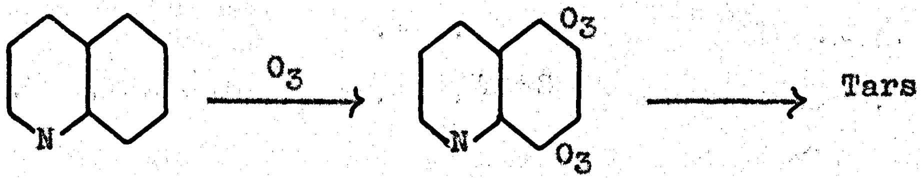
145 g. (1 mole)	167.1 g. (1 mole)	166.1 g. (1 mole)
20 g. (0.155 mole)	11.4 g. (0.068 mole)	12.8 g. (0.077 mole)

$$\% \text{ Yield - Quinolinic Acid} = \frac{0.068}{0.115} = 44.0\%$$

$$\% \text{ Yield - Phthalic Acid} = \frac{0.077}{0.155} = 49.5\%$$

A solution of 20.0 g. (0.155 mole) of isoquinoline in 200 ml. of glacial acetic acid was ozonized as previously described. If a small amount of water was added to the solvent, cinchomeronic acid (11.4 g., 44.0%), m.p. 259-60° C., precipitated from solution during the ozonization. The solid material was separated by filtration and the filtrate refluxed with 35 g. of 30% hydrogen peroxide for two hours. Evaporation to dryness (or continuous ether extraction) of the resulting solution yielded 12.8 g. (49.5%) of phthalic acid, m.p. 204-205° C., and small amounts of cinchomeronic acid. The yield of cinchomeronic acid was lowered to 10% when the ozonization time was reduced to twelve hours.

C. Ozonization of Quinoline:



145 g. (1 mole)

72.5 g. (0.5 mole)

The ozonization was conducted as previously described. The solvent was removed under vacuum and the resulting product was refluxed, in turn, with water; concentrated hydrochloric acid; glacial acetic acid;

zinc, stannous chloride, and hydrochloric acid; 30% hydrogen peroxide; and concentrated nitric acid. Traces of quinolinic acid were isolated only in the last two cases, as well as upon low pressure catalytic hydrogenation with 5% palladium on charcoal, and subsequent treatment with 30% hydrogen peroxide. The addition compound, upon steam distillation in a basic solution, did not produce any unreacted quinoline. Attempts to distill the compound under low pressures failed; the major part of the material formed a tar, while, to a lesser extent, quinoline and ozone were regenerated. The ozone was detected by the formation of a sodium hydroxide ozonate*, which results from the action of ozone on solid sodium hydroxide and liberates oxygen when placed in an acid solution.

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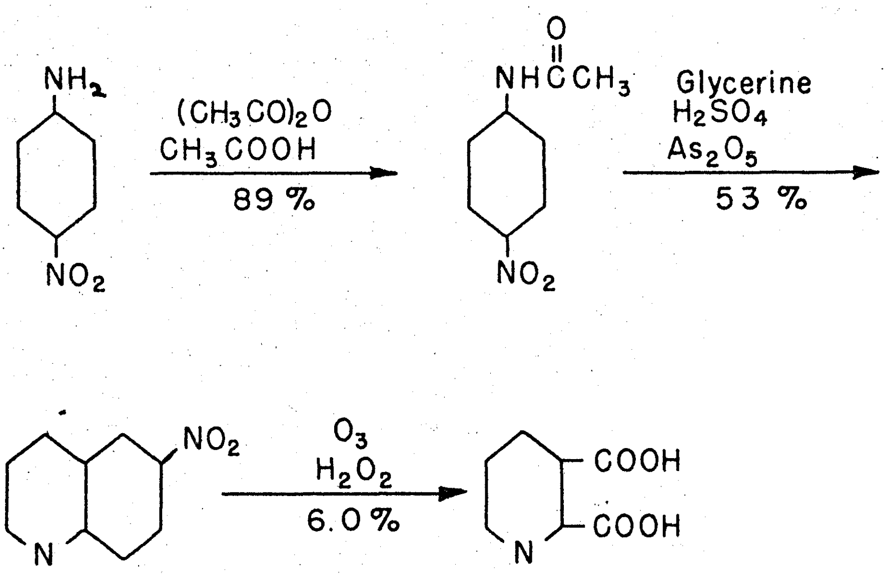
* A study of sodium hydroxide ozonates is being conducted in the laboratory by Mr. Thomas Whaley.

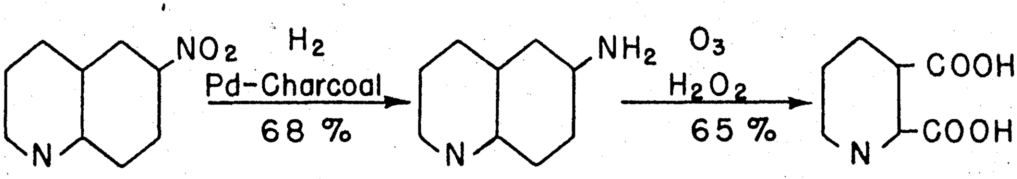
EXPERIMENTAL

II - Synthesis and Ozonization of Nitro- and Amino-Substituted Quinolines

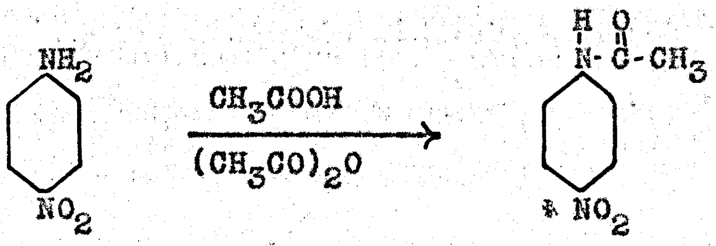
6-Nitroquinoline:



6 - Aminoquinoline:



D. <u>Preparation of p-Nitroacetanilide:</u>

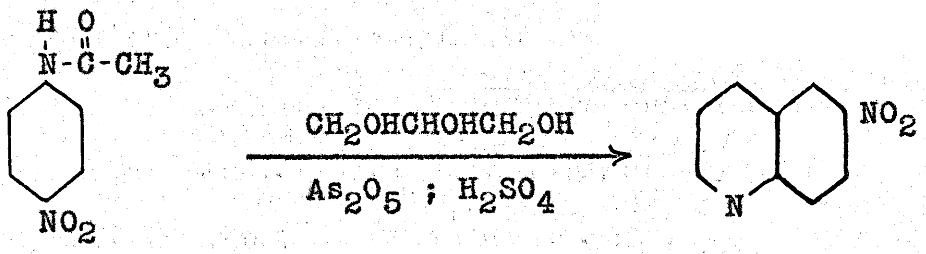


138.1 g. (1 mole)	180.2 g. (1 mole)
276.0 g. (2 moles)	332 g. (1.85 moles)

$$\% \text{ Yield} = \frac{1.85}{2.00} = 92.5\%$$

A 3-liter flask was charged with 1000 cc. of glacial acetic acid and 500 cc. of acetic anhydride, and 276 g. (2.0 moles) of p-nitroaniline was slowly added, with agitation and cooling. The mixture was heated on a steam bath for one and one-half hours, with frequent shaking, and was then poured into a large excess of cold water. The solids were filtered and washed, first with a dilute hydrochloric acid solution, then with water. The yield of p-nitroacetanilide, m.p. 214-15° C., was 332 g. (92.5%).

E. Preparation of 6-Nitroquinoline:

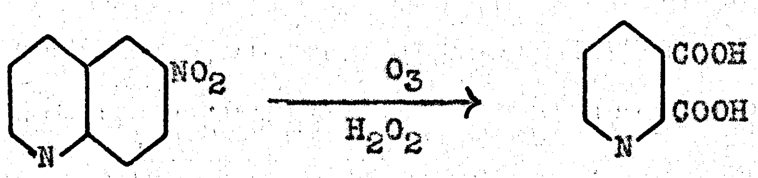


180.2 g.(1 mole)	174.2 g. (1 mole)
332 g. (1.84 moles)	170 g. (0.975 mole)

$$\% \text{ Yield} = \frac{0.975}{1.84} = 53.0\%$$

A 5-liter flask equipped with a stirrer, thermometer, and reflux condenser was charged with 332 g. (1.84 moles) of p-nitroacetanilide, 736 g. (8 moles) of glycerine, and 244 g. (1.50 moles) of arsenic pentoxide. Then 800 g. of concentrated sulfuric acid was added slowly, at such a rate that the temperature did not exceed 125° C. The mixture was then heated, with agitation, for four hours at 130° C., cooled, and diluted with 5 liters of water. The solution was heated with 100 g. of Norite for one hour, and the decolorized product obtained by filtration. This was followed by neutralization of the filtrate with aqueous ammonia. After several recrystallizations from alcohol-water, the yield of 6-nitroquinoline, m.p. 149-50° C., was 170 g. (53.0%).

F. Ozonization of 6-Nitroquinoline:

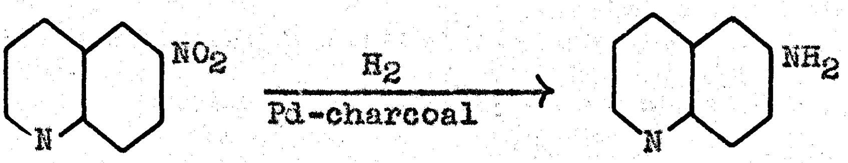


174.2 g. (1 mole)	167.1 g. (1 mole)
8.7 g. (0.05 mole)	0.5 g. (0.003 mole)

$$\% \text{ Yield} = \frac{0.003}{0.05} = 6.0\%$$

A solution containing 8.7 g. (0.05 mole) of 6-nitroquinoline in 200 ml. of commercial glacial acetic acid was subjected for forty-eight hours, at room temperature, to a stream of 9-10% ozonated oxygen, flowing at 20 liters per hour. Upon completion of the run, the walls of the reaction vessel were coated with 0.5 g. of a white solid material (quinolinic acid), m.p. 189-90° C. with decomposition, remelting at 225-6° C., yield - 6.0%. The ozonated solution was added to a solution of 50 ml. of water and 30 g. of 30% hydrogen peroxide, then refluxed for two hours and concentrated by evaporation. An oil was obtained, which was made basic and extracted with ether. 3.5 g. of unreacted 6-nitroquinoline and some unidentified tarry material were obtained. (No nitrophthalic acid could be isolated.)

G. Preparation of 6-Aminoquinoline:

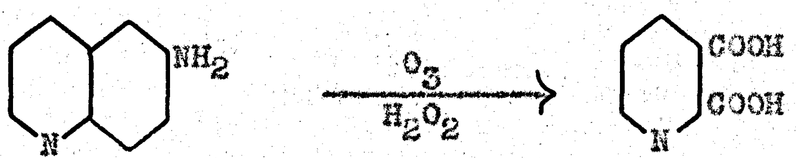


174.2 g. (1 mole)	144.2 g. (1 mole)
112 g. (0.642 mole)	63 g. (0.437 mole)

$$\% \text{ Yield} = \frac{0.437}{0.642} = 68.0\%$$

A solution of 112 g. (0.642 mole) of 6-nitroquinoline in 800 cc. of absolute alcohol was hydrogenated under a pressure of two atmospheres, in the presence of 3.0 g. of 2% palladium-charcoal catalyst. When the hydrogen absorption ceased,(81% of the theoretical value absorbed), the catalyst was filtered and the alcohol removed by distillation. The yield of 6-aminoquinoline, m.p. 116-17° C., was 63 g. (68.0%).

H. Ozonization of 6-Aminoquinoline:



144.2 g. (1 mole)	167.1 g. (1 mole)
4.0 g. (0.0276 mole)	3.0 g. (0.0179 mole)

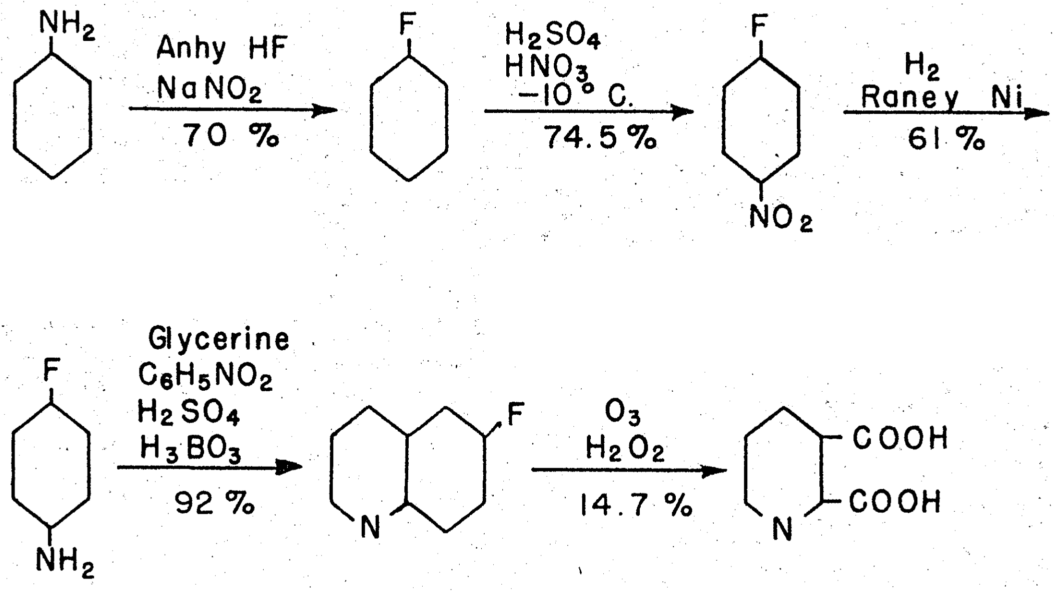
$$\% \text{ Yield} = \frac{0.0179}{0.0276} = 65.0\%$$

A solution containing 4.0 g. (0.0276 mole) of 6-aminoquinoline in 200 cc. of commercial glacial acetic acid was subjected for forty-eight hours, at room temperature, to a stream of 9-10% ozonated oxygen, flowing at 20 liters per hour. Upon ozonization, the solution darkened, but gradually turned a light yellow color. Upon completion of the run, the walls of the reaction flask were coated with 1.2 g. of a solid acid, which, upon recrystallization from hot water, melted with decomposition at 190-1° C. and remelted at 225-6° C. (Quinolinic acid.) The remaining ozonated solution was refluxed for two hours with 50 cc. of water and 10 g. of 30% hydrogen peroxide. The resulting solution was concentrated by evaporation and 1.8 g. of quinolinic acid was isolated. Total yield was 2.0 g., (65.0%).

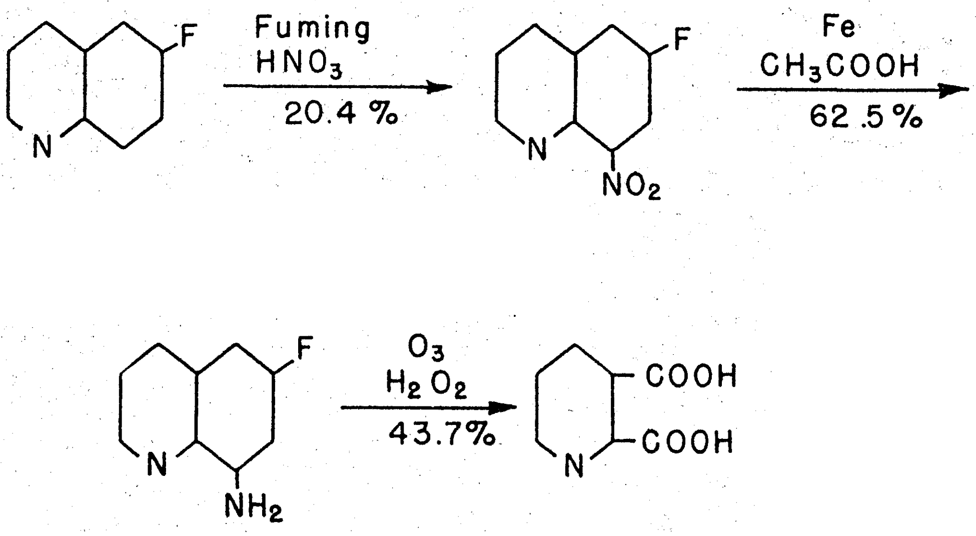
EXPERIMENTAL

III - Synthesis and Ozonization of Fluoro-and Amino-Substituted Quinolines

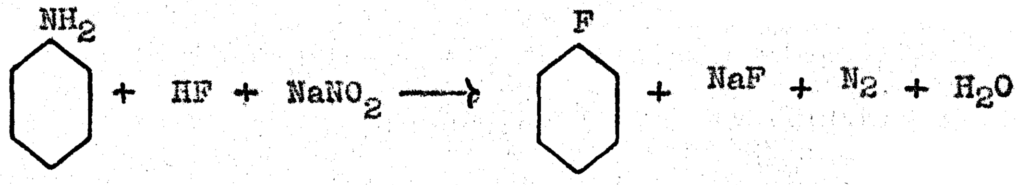
6-Fluoroquinoline:



6-Fluoro-8-Aminoquinoline:



I. Preparation of Fluorobenzene:



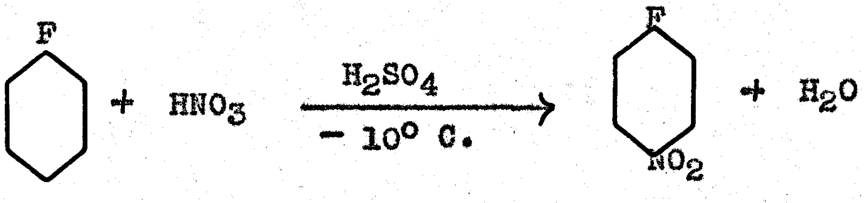
93.1 g. (1 mole)	96.1 g. (1 mole)
279 g. (3 moles)	202 g. (2.10 moles)

$$\% \text{ Yield} = \frac{2.10}{3.00} = 70.0\%$$

A chrome-steel 2-liter reaction flask was charged with 279 g. (3.0 moles) of freshly distilled aniline, and 1000 g. (50 moles) of anhydrous hydrogen fluoride was slowly added, with agitation, at 0° C. To this mixture, 250.5 g. (3.6 moles) of sodium nitrite was added, with agitation, at such a rate that the temperature did not exceed 10° C. The reaction mixture was stirred for an additional hour and was then connected to an ice-cooled copper reflux coil and allowed to stand overnight at room temperature.

The mixture was then diluted with 600 g. of ice and steam-distilled. The insoluble oil was collected, washed with 5% sodium carbonate solution, dried over calcium chloride, and fractionated. The yield of fluorobenzene, b.p. 84-5° C. at 735 mm., was 202 g. (70.0%).

J. Preparation of p-Nitrofluorobenzene:

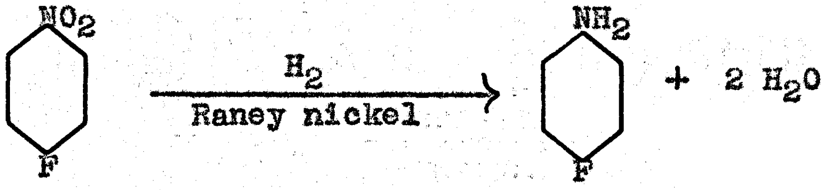


96.1 g. (1 mole)	141.1 g. (1 mole)
245 g. (2.55 moles)	268 g. (1.90 moles)

$$\% \text{ Yield} = \frac{1.90}{2.55} = 74.5\%$$

A 2-liter flask equipped with a dropping funnel and a stirrer was charged with 175 cc. of fuming nitric acid (Sp.G. 1.5) and 350 cc. of concentrated sulfuric acid. With vigorous agitation, 245 g. (2.55 moles) of fluorobenzene was added dropwise, at -10° C. The reaction mixture, which became very viscous, was poured on ice, extracted with ether, and fractionated. The yield of p-nitrofluorobenzene, b.p. 114-5° C. at 40 mm. pressure, was 268 g. (74.5%).

K. <u>Preparation of p-Fluoroaniline</u>:

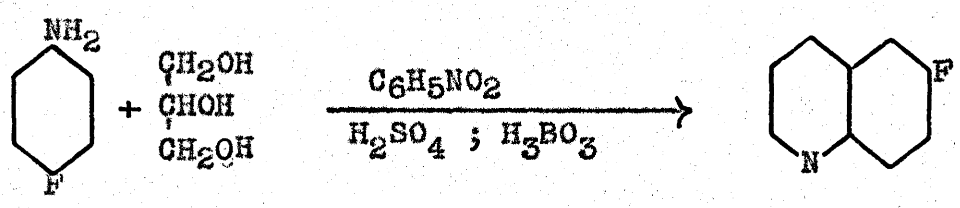


141.1 g. (1 mole)	111.1 g. (1 mole)
229 g. (1.62 moles)	110 g. (0.99 mole)

$$\% \text{ Yield} = \frac{0.99}{1.62} = 61.0\%$$

A solution of 229 g. (1.62 moles) of p-nitrofluorobenzene in 350 cc. of absolute alcohol was hydrogenated at low pressure in the presence of Raney nickel catalyst and a trace of chloroplatinic acid as a promoter. Heat was applied to initiate the reaction. When absorption of hydrogen ceased (93% of the theoretical amount absorbed), the catalyst was removed by filtration and the alcohol by distillation. The residue was dissolved in aqueous hydrochloric acid, extracted with ether to remove non-basic material, neutralized with sodium hydroxide, and again extracted with ether. The ether extract was dried over sodium sulfate, and filtered; the ether was removed by distillation. Fractional distillation of the residue gave 110 g. (61.0%) of p-fluoroaniline, b.p. 97-8° C. at 28 mm.

L. Preparation of 6-Fluoroquinoline:



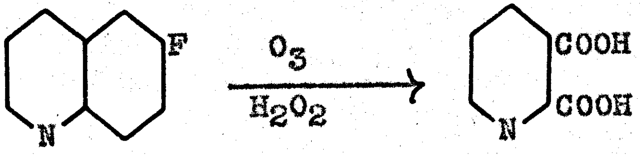
111.1 g. (1 mole)	147.2 g. (1 mole)
110 g. (0.99 mole)	134 g. (0.91 mole)

$$\% \text{ Yield} = \frac{0.91}{0.99} = 92.0 \%$$

To a 3-liter flask containing 31.5 g. of ferrous sulfate, 110 g. (0.99 mole) of p-fluoroaniline and 66.4 g. (0.54 mole) of nitrobenzene, a cold solution of 55.6 g. (0.9 mole) of boric acid in 332 g. of glycerol was added. (The boric acid had previously been dissolved in the glycerol by gentle heating.) Then 155 ml. of 95% sulfuric acid was added slowly, with cooling. The contents of the flask were mixed, connected with a reflux condenser, heated over a free flame until the boiling point was reached, and refluxed for twenty-four hours.

The mixture was cooled, neutralized with 565 cc. of 60% sodium hydroxide solution, and steam-distilled. The distillate was extracted with ether; the ether was dried and removed by distillation, and the residue was fractionated. The yield of 6-fluoroquinoline, b.p. 125-6 °C. at a pressure of 30 mm., was 134 g. (92.0%)

M. Ozonization of 6-Fluoroquinoline:

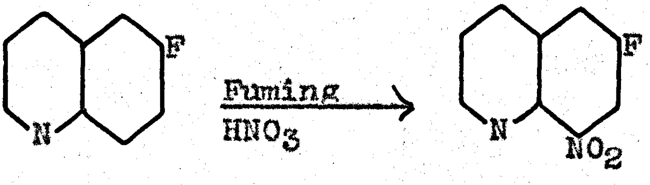


147.2 g. (1 mole)	167.1 g. (1 mole)
15 g. (0.102 mole)	2.5 g. (0.0150 mole)

$$\% \text{ Yield} = \frac{0.015}{0.102} = 14.7\%$$

A solution containing 15 g. (0.102 mole) of 6-fluoroquinoline in 200 cc. of commercial glacial acetic acid was subjected for forty-eight hours, at room temperature, to a stream of 9-10% ozonated oxygen flowing at 20 liters per hour. Upon completion of the run, the walls of the reaction flask were coated with 2.5 g. of a light yellow solid, which, upon recrystallization from hot water, melted with decomposition at 190-1° C. and remelted at 225-6° C. (Quinolinic acid.) The yield was 14.7%. The ozonated solution was refluxed for two hours with 50 cc. of water and 20 g. of 30% hydrogen peroxide. The resulting solution was concentrated by evaporation and made alkaline. Ether extraction yielded 6.5 g. of unreacted 6-fluoroquinoline. An unidentified tarry material was also obtained.

N. Preparation of 6-Fluoro-8-Nitroquinoline:

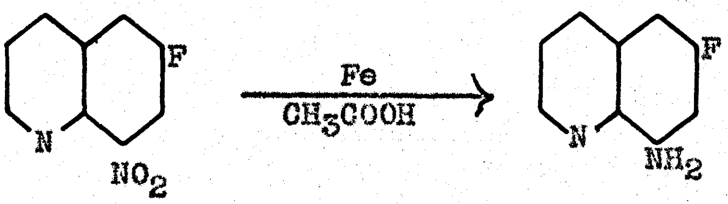


147.2 g. (1 mole)	192.2 g. (1 mole)
150 g. (1.02 moles)	40 g. (0.280 mole)

$$\% \text{ Yield} = \frac{0.280}{1.02} = 20.4\%$$

A 2-liter flask was charged with 660 ml. of fuming nitric acid (Sp.G. 1.5) and 150 g. (1.02 moles) of 6-fluoroquinoline, and the mixture refluxed for eighty hours. It was then poured on ice and treated with aqueous ammonia until just neutral to litmus. The yellow flocculent precipitate produced was filtered to yield 80 g. of crude product, which was repeatedly recrystallized from 95% alcohol to yield 40 g. of 6-fluoro-8-nitroquinoline, m.p. 117-8° C. Approximately 40 g. of unreacted 6-fluoroquinoline was recovered. The yield was 20.4%, based on the starting material; 37.4%, based on that which reacted.

O. Preparation of 6-Fluoro-8-Aminoquinoline:

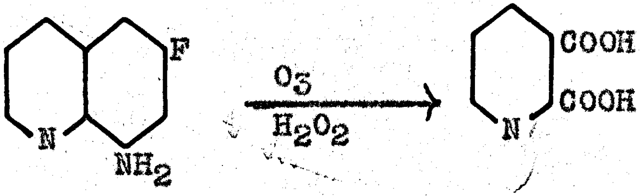


192.2 g. (1 mole)	162.2 g. (1 mole)
38 g. (0.197 mole)	20 g. (0.123 mole)

$$\%\ \text{Yield} = \frac{0.123}{0.197} = 62.5\%$$

In a 3-liter flask, 38 g. (0.197 mole) of 6-fluoro-8nitroquinoline was dissolved in 1000 ml. of 50% aqueous acetic acid, and 61 g. of finely divided powdered iron was slowly added, with vigorous agitation, over a period of two hours. The mixture was warmed on a steam bath during the addition of the iron powder and was then heated for two additional hours. The entire mixture was made strongly basic with sodium hydroxide and was steam-distilled. A white flocculent solid precipitated from the distillate upon cooling. The yield of 6-fluoro-8-aminoquinoline, m.p. 50-1° C., was 20 g. (62.5%).

P. Ozonization of 6-Fluoro-8-Aminoquinoline:



162.2 g. (1 mole) 167.1 g. (1 mole)

4.0 g. (0.0247 mole) 1.8 g. (0.0108 mole)

$$\% \text{ Yield} = \frac{0.0108}{0.0247} = 43.7\%$$

A solution containing 4.0 g. (0.0247 mole) of 6-fluoro-8-aminoquinoline in 200 cc. of commercial glacial acetic acid was subjected for forty-eight hours, at room temperature, to a stream of 9-10% ozonated oxygen flowing at 20 liters per hour. Upon ozonization, the solution darkened, but gradually turned a light yellow color at the end of the run. No solid material precipitated during the ozonization. The solvent was partially removed under vacuum, and the remaining solution was refluxed for two hours with 10 g. of 30% hydrogen peroxide. Concentration by evaporation yielded 1.8 g. (43.7%) of a solid acid, which, after recrystallization from hot water, melted with decomposition at 190-1° C. and remelted at 225-6° C.

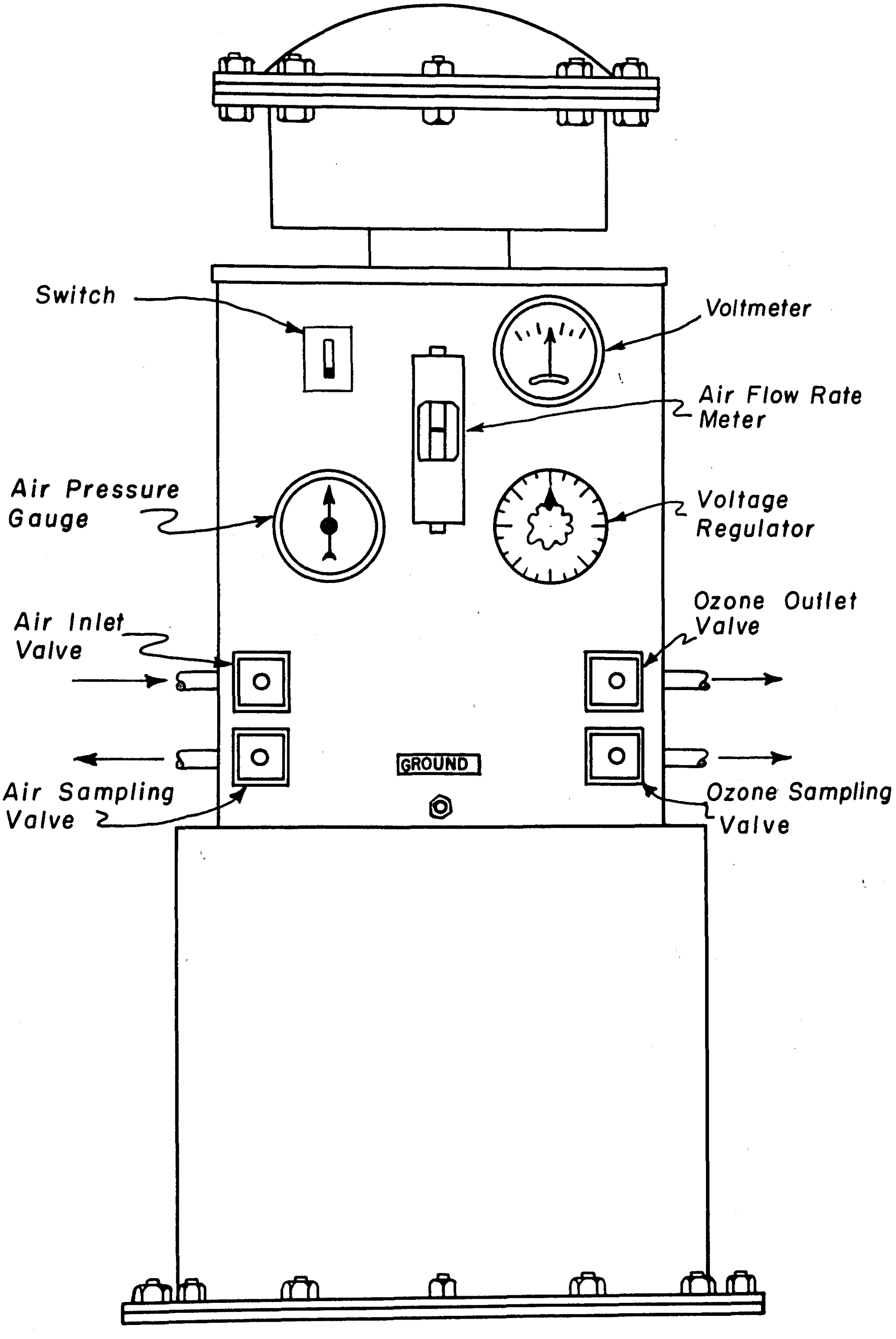
IV. THE OZONATOR

The ozonator (Fig. I) used in this investigation was purchased from OZONE PROCESSES, INC., Philadelphia, Pa. The Ozonator, type T-12, was designed for operation on a 115-volt, 60-cycle A. C. circuit. The transformer within the steel shell possesses a voltage ratio, primary to secondary, of 1:130, with a maximum secondary voltage of approximately 16,000 volts. To compensate for fluctuations in the line voltage, a variable voltage transformer has been incorporated into the primary circuit. The output voltage from the transformer is recorded on a panel voltmeter. The ozonator is so constructed that the voltage as indicated on the voltmeter should never be set above 120 volts when operating on air, and 110 volts when operating on oxygen. A safety pressure switch in series with the ozonator's primary circuit opens the circuit when the pressure inside the ozonator tank falls below 3 pounds per square inch (gauge).

Whenever the ozonator is in operation, a flow of water should be maintained through the cooling jacket. The ground terminal on the ozonator panel must be connected to a solid electrical ground. The oxygen pressure should be maintained at 8 pounds per square inch by means of a suitable reducing valve preceding the ozonator.

Figure I

The Ozonator



The oxygen inlet valve is left open and the gas flow regulated by throttling the ozone outlet valve. The flow is read directly from the rotometer on the panel board. The rotometer has been calibrated at 8 pounds per square inch pressure, and reads in cubic feet per minute. The ozonator also possesses an oxygen and an ozone sampling valve, through which oxygen and ozone may be bled during various stages of the run to determine ozone concentration, moisture content, etc.

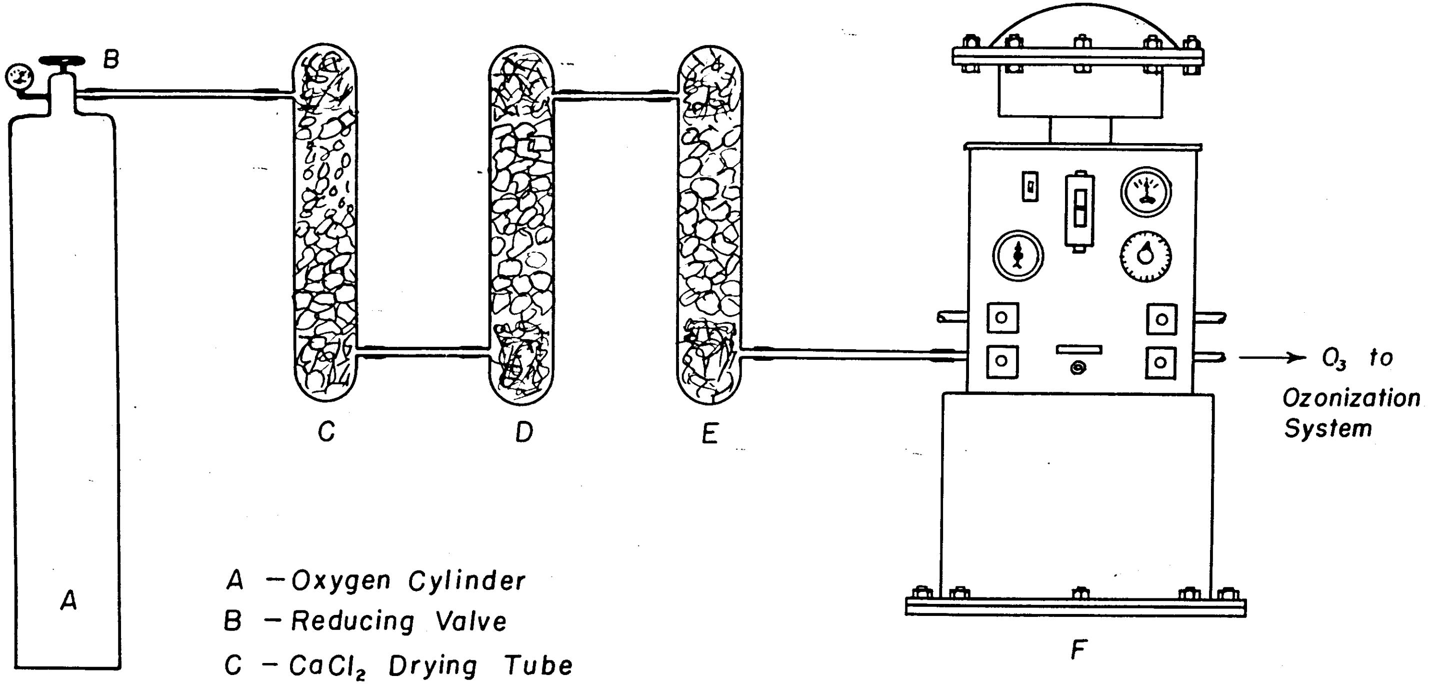
A. Purification Train

Before the oxygen was ozonized, it was passed through a purification train (Fig. II) in order to remove all traces of moisture and impurities. The oxygen was supplied to the system from a cylinder (A), via a high pressure reducing valve (B). Connected to the high pressure reducing valve were three drying towers in series, two containing anhydrous calcium chloride (C, D), and the third, anhydrous magnesium perchlorate (E).

The oxygen passed from the purification train into the ozonator, where the pressure and the desired flow were adjusted and recorded on the ozonator's low pressure rotometer. Rubber tubing was first used for connections in the purification train, but the ozone eventually attacked the rubber, and tygon tubing was found to be most desirable. A rapid stream of oxygen was passed through the purification train for thirty

Figure II

Purification Train



A – Oxygen Cylinder
B – Reducing Valve
C – $CaCl_2$ Drying Tube
D – $CaCl_2$ Drying Tube
E – $Mg(ClO_4)_2$ Drying Tube
F – Ozonator

minutes before initial use in order to blow out all the dust particles and to test for leaks.

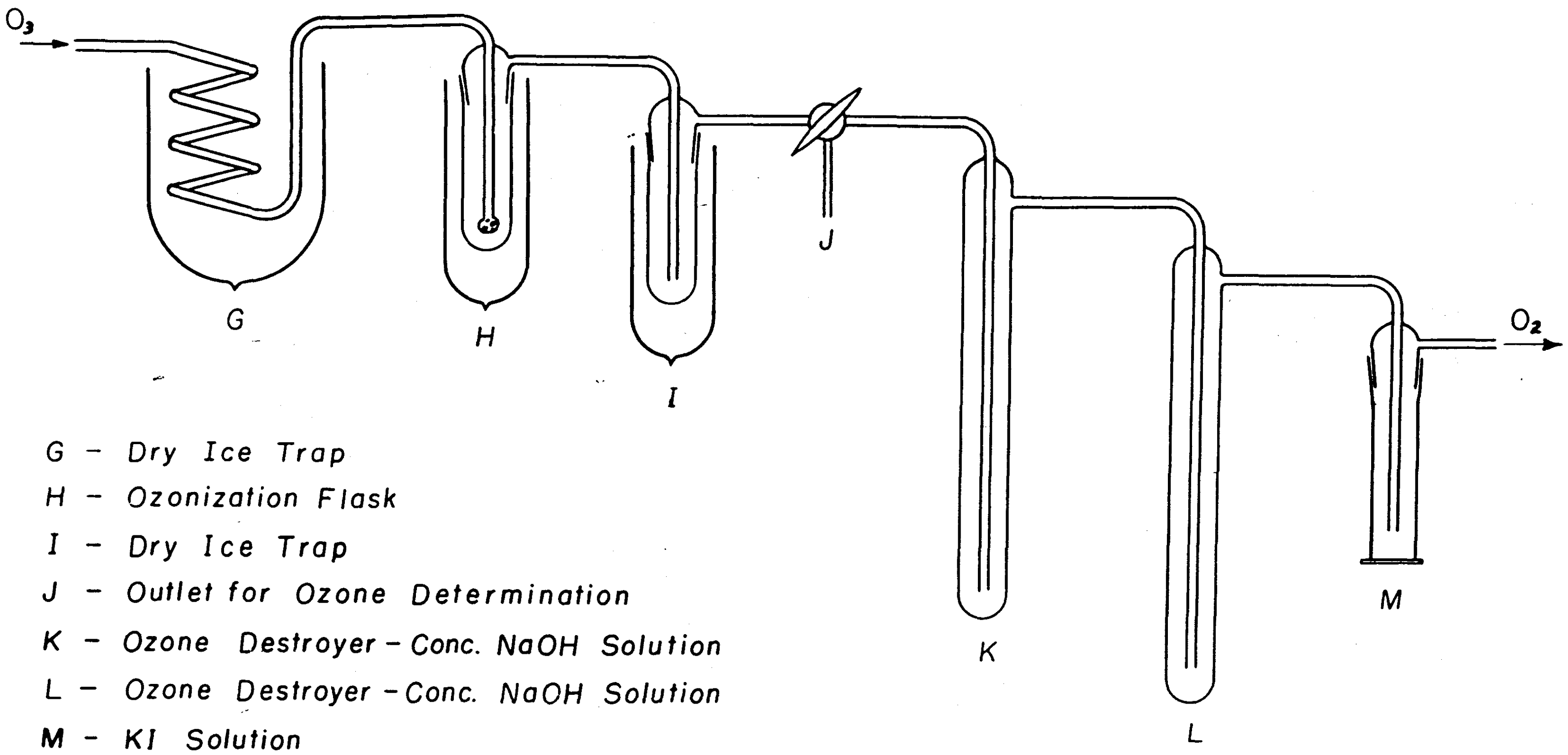
B. Ozone Absorption Assembly

The ozone produced by the ozonator (Fig. III) was passed through a dry ice trap (G), and then led to the reaction vessel (H), which was surrounded by a cooling bath. Connected to the reaction vessel was a condensing tube surrounded by acetone and dry ice (I), to trap any volatile compounds or solvent escaping from the reaction vessel. A third flask was connected in this series to absorb and make possible a determination of the amount of unreacted ozone which left the reaction flask (J). All parts carrying ozone were connected either by ground glass joints or tygon tubing. An ozone-destroying unit consisting of two 30-inch towers filled with 20% aqueous sodium hydroxide was connected in series (K, L). The oxygen leaving the system was then passed through a KI solution (M) as a final indication of complete ozone decomposition.

Ozone is a powerful irritant, and the maximum working concentration is 0.15 to 1.0 parts per million of air. It was therefore necessary to destroy any excess ozone and to ventilate the room thoroughly. The entire ozone absorption assembly and the ozone destroying unit were placed in an efficient hood.

Figure III

Ozonization System



G - Dry Ice Trap
H - Ozonization Flask
I - Dry Ice Trap
J - Outlet for Ozone Determination
K - Ozone Destroyer - Conc. NaOH Solution
L - Ozone Destroyer - Conc. NaOH Solution
M - KI Solution

C. Adjusting Ozone Concentrations

The concentration of ozone in air or oxygen can be increased or decreased by increasing or decreasing the voltage between the operating limits of about 70 volts to 110 volts when using oxygen, and 70 to 120 volts when using air in the ozonator. The concentration can be further varied by decreasing or increasing the gas flow through the ozonator, varying the temperature of the cooling water, the gas pressure, or the dew point of the gas.

The maximum concentration obtainable depends upon the cooling water temperature to a large extent, with higher concentrations possible at lower cooling water temperatures. Air dryness and equilibrium conditions inside the ozonator are also of particular importance. For instance, if the glass tube inside the ozonator is exposed to atmospheric or improperly dried air and subsequently operated with dry oxygen, it will take 36-48 hours to bring the ozonator to equilibrium conditions and maximum output.

For these reasons, it is desirable to keep all conditions as constant as possible. In general, it is not possible to calibrate the concentration or output against voltage, even if the above conditions are held seemingly constant, since other uncontrollable conditions will cause variation. Thus, ozone concentrations are usually measured by bleeding off a small amount of ozone during the time ozone passes into the material to be treated.

D. Measuring Ozone Concentration

The ozone concentration is measured by sweeping out the apparatus for five minutes with ozone, which is led to the ozone destroyer. Ozone is then led into the reaction vessel containing a 5% solution of potassium iodide. The time and flowmeter readings are recorded and the resulting solution acidified with 10% sulfuric acid. The free iodine which is liberated by the ozone is titrated with a standardized 0.2 N sodium thiosulfate solution with starch as the indicator.

$$H_2O + 2\ KI + O_3 \longrightarrow 2\ KOH + O_2 + I_2$$

Such determinations may be made at different voltages and rates of flow, and the data summarized and plotted to give approximate time and flow relationships for any concentration of ozone desired.

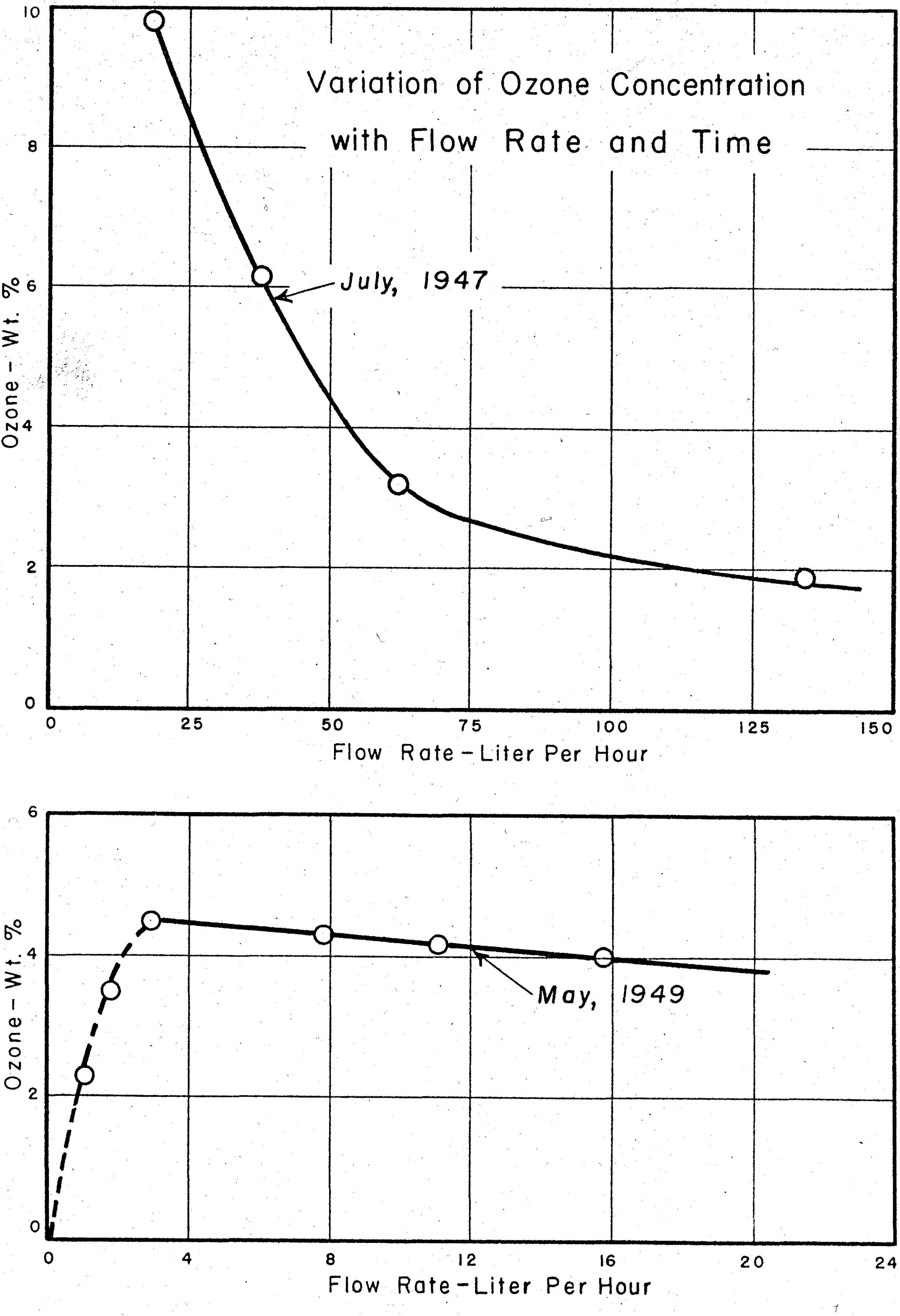
When air is the source of oxygen, the exit gases from the ozonator contain lower percentages of ozone than when pure oxygen is used. The gases also contain small amounts of nitric anhydride or nitrogen pentoxide, depending on the voltage used. A decrease in the rate of flow increases the amount of nitrogen pentoxide, but such amounts are relatively low and need only be considered when examining a reaction mixture for small amounts of by-products, or when the presence of such oxides causes a catalytic effect on the oxidation of the organic compounds in the reaction.

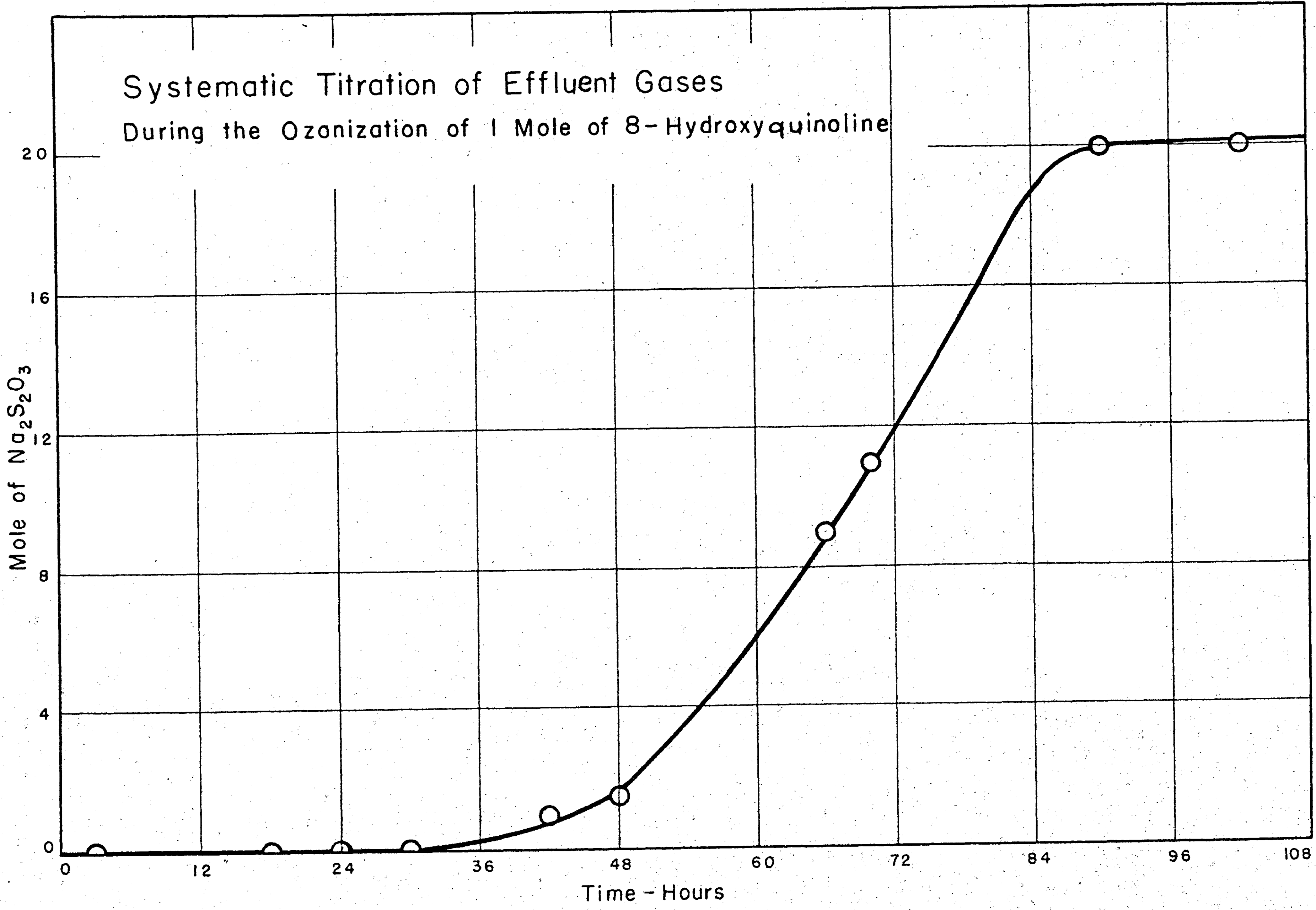
Ozone concentration determinations on the T-12 ozonator used in this work were made at a voltage of 110 volts, the maximum voltage specified for the use of oxygen, and with varying rates of flow (July, 1947). (See Table I)

TABLE I

TIME (seconds)	ROTOMETER READING (C.F.M.)	FLOW (liters/hr.)	$Na_2S_6O_3$ (0.2380 N)	OZONE (g./hr)	OZONE (volume %)
60	0.00	18	7.6 ml	2.6	9.8%
60	0.02	33.5	8.9 ml	3.0	6.2%
60	0.04	67	10.2 ml	3.5	3.2%
60	0.08	134	12.0 ml	4.1	1.9%

The pressure and cooling water temperatures were maintained constant at 8 p.s.i. and 15° C. respectively, and the ozonator was operated for 48 hours to obtain equilibrium conditions. The ozone concentrations were determined again in May, 1949, at low flow rates. (See plot on following page.) A considerable decrease in the ozone


Variation of Ozone Concentration
with Flow Rate and Time
10
8
6
4
2
0
Ozone - Wt. %
July, 1947
0
25
50
75
100
125
150
Flow Rate - Liter Per Hour
6
4
2
0
Ozone - Wt. %
May, 1949
0
4
8
12
16
20
24
Flow Rate - Liter Per Hour



Systematic Titration of Effluent Gases

During the Ozonization of 1 Mole of 8-Hydroxyquinoline concentration was noted (9-10% to 4-5%) under similar operating conditions.

The maximum ozone output designated by OZONE PROCESSES, INC. is 20 mg. per liter or 4 g. per hour at a flow rate of 200 liters per hour. This is a weight percentage of 1.3% ozone. The maximum concentration for practical working conditions is about 60 mg. per liter or 1.0 g. per hour at a flow rate of 17 liters per hour. This corresponds to a weight concentration of 4.0%. Higher concentrations can be obtained, as shown above, under optimum conditions.

V. DISCUSSION OF RESULTS

Ozonization of Quinoline:

Concentrations of quinoline varying up to 20% were subjected to a stream of (5-10%) ozonated oxygen at flow rates from 20 to 80 liters per hour. Dry ethyl acetate or glacial acetic acid were used as the solvent with comparable success. By systematic titration of the effluent gases it was found that at low flow rates one mole of ozone was readily fixed, whereupon further addition of ozone to form a diozonide was considerably slower. The curve obtained by plotting time vs. ozone concentration flattens when ozone is no longer absorbed by the reacting solution.

In all cases the ozonide formed was unusually stable, resisting decomposition, even under drastic conditions, by reagents commonly employed for decomposing ozonides, such as water, steam, concentrated sodium hydroxide solutions, concentrated hydrochloric acid, glacial acetic acid and zinc, stannous chloride and hydrochloric acid, 30% hydrogen peroxide, and concentrated nitric acid. Traces of quinolinic acid were isolated only in the last two cases, as well as upon low pressure catalytic hydrogenation with 5% palladium on charcoal and subsequent treatment with 30% hydrogen peroxide. The addition compound, upon steam distillation in a basic solution, did not produce any unreacted quinoline. Attempts to distill the compound under low pressures failed, the preponderance of the material forming a tar, while, to a lesser extent, quinoline and ozone were regenerated. The ozone was detected by the formation of a sodium hydroxide ozonate, which results from the action of ozone on solid sodium hydroxide and which liberates oxygen when placed in an acid solution.

Temperature effects upon the ozonization of quinoline were not critical, and successful ozonizations were conducted between 0° and 70° C. Most of the ozonization reactions involving quinoline were conducted at room temperature, due to convenience.

One may postulate that the ozone should attack the benzene nucleus, as the ring nitrogen is capable of exhibiting a —T effect, decreasing the electron density of the pyridine ring and thus, in comparison, increasing the electron density in the benzene ring. Likewise, during acid oxidation of quinoline, this —T effect is strong and quinolinic acid is the main product. However, lack of desired product and incomplete identification of the ozonide results in failure to substantiate any postulation.

Ozonization of 8-Hydroxyquinoline:

Solutions consisting of 8-hydroxyquinoline in ethyl acetate and glacial acetic acid were ozonized under various conditions. Glacial acetic acid appeared to give the best results and, in general, was the most suitable. The ozonization proceeded nicely at room temperature, but a cooling bath was needed when large quantities (1.) mole) of 8-hydroxyquinoline was ozonized at one time, due to heat evolved by partial decomposition of the ozonide in solution, resulting from traces of water. Yields of quinolinic acid as high as 30-40% were obtained from the reaction solution by such decomposition.

Ozone concentrations of 10% were most effective but suitable ozonizations were conducted using as low as 2-3% ozone, by extending the ozonization time. The ozonization reaction and the end point can readily be followed by systematic titration of the effluent gases. Ozone is added quantitatively during the (P-48) reaction of a large part of the first double bond, but then the reaction rate decreases and the remaining addition is slow and not quantitative.

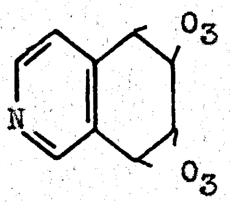
Ozone oxidation of 8-hydroxyquinoline consistently gave 90-95% yields of quinolinic acid. The ozonide, in contrast to that of quinoline, was very reactive and could be cleaved by both hydrogen peroxide and water. Because it gave a cleaner, facile reaction, hydrogen peroxide in acid solution was consistently used in preference to hot water. Decomposition, in every case, could be accomplished merely by treatment with hot water, but the reaction was slower, with yields of approximately 70%.

The effect of the strong electron-donating hydroxyl group on the benzene nucleus and the —T effect exhibited by the ring nitrogen undoubtedly places a high electron density on the benzene nucleus. Thus the ozonization proceeded readily, with attack on the benzene nucleus, until the first double bond had reacted. Then a slight hindering effect could be observed by the hydroxyl group, as ozone adds less readily to a carbon-carbon double bond which possess other substituents than an unsubstituted carbon-carbon double bond. However, the presence of the hydroxyl group resulted in a very desirable decrease in the stability of the resulting ozonide, to a point where the ozonide could be readily decomposed by either hydrogen peroxide or water to give good yields of quinolinic acid.

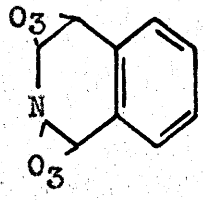
Ozonization of Isoquinoline:

Ozone added relatively slowly to isoquinoline, forming diozonides. The diozonide formed by the attack of ozone on the benzene nucleus was reactive in comparison with the unsubstituted quinoline diozonide, decomposing directly, in solution, to yield cinchomeronic acid, if small amounts of water were present. Treatment of the remaining ozonated solution with 30% hydrogen peroxide yielded phthalic acid and small amounts of cinchomeronic acid, indicating that, in marked contrast to its action on quinoline, ozone attacked both the benzene and pyridine rings.

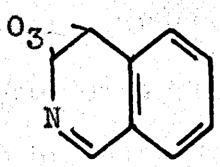
The ease of decomposition of the isoquinoline diozonide in which the ozone has attacked the benzene nucleus is difficult to explain, in comparison to the stability of the quinoline diozonide or the ozonide resulting from the attack of ozone on the pyridine nucleus of isoquinoline. However, the carbon-carbon double bond is known to react with ozone more readily than the carbon-nitrogen double bond, and the ring nitrogen is capable of exhibiting a —T effect, which tends, in comparison, to increase the electron density of the benzene nucleus, making ozone attack most likely on the benzene nucleus (A). The possibility



A



B



C

of the formation of a diozonide on the pyridine nucleus (B) is therefore not as likely as a monoozonide (C), which would also be more stable than the diozonide and possibly would not decompose in solution by mere contact with water. As 45 and 50% yields of quinoline and phthalic acids, respectively, have been obtained, it appears that the —T effect of the nitrogen is small and that the electron density on the two rings is comparable, resulting in equal initial attack of ozone on both rings.

Conditions investigated indicated that ozonization of isoquinoline in acetic acid containing small amounts of water, at room temperature, using high ozone concentrations (10%), yields the best results and is the easiest means of separation, since cinchomeronic acid precipitates from the reacting solution. Additional cinchomeronic acid and phthalic acid are obtained by treating the reaction solution with hydrogen peroxide.

Ozonization of Other Quinoline Derivatives:

Quinoline derivatives bearing one or more substituents in the benzene ring added ozone less readily than quinoline itself, particularly if the substituents were electron-withdrawing in nature. All gave quinolinic acid as the only identifiable product, in poor yield if the substituents were electron-withdrawing, in good yield if they were electron-releasing. 6-amino-, 6-fluoro-8-amino-, 6-fluoro-, and 6-nitro-quinoline yielded 65, 44, 15, and 6% quinolinic acid, respectively. Tarry oxidation products were also formed, and, in the last two cases, almost half of the quinolines were recovered unchanged.

The fact that quinolinic acid was the only identifiable product in the ozonization of 6-nitroquinoline was quite unexpected. One would anticipate obtaining some nitrophthalic acid, as the strong electron-withdrawing nitro group should counteract the —T effect of the ring nitrogen, thus increasing the electron density of the pyridine ring, or at least equalizing the two rings. However, all of these results substantiate the observation that the pyridine ring in quinoline is much more resistant to oxidation than the benzene ring.

VI. SUGGESTIONS FOR FUTURE WORK

A. Completion of Work Started:

Proposed suggestions for extension of work already started are as follows:

Ozonization of Acridine: The continued study of the ozonization of acridine and its substituted derivatives.

Acridine possesses four double bonds capable of being ozonated, and therefore presents an interesting problem in the production and isolation of acridinic acid and pyridine-tetracarboxylic acid or pyridine-tricarboxylic acid, the former being prepared by the controlled ozonization of substituted acridines and the latter by the complete ozonization of acridine. Preliminary uncontrolled experiments in this field have yielded small amounts of acridinic acid, while the more promising ozonization of substituted acridines has not been investigated.

Vapor Phase Ozonization: The study of the feasibility of vapor phase ozonizations of volatile olefines:

Vapor phase ozonizations show promise due to their elimination of selecting suitable solvents, working at low temperatures, isolation and handling of explosive ozonides, and also because of their possible commercial application to a continuous process.

It has been found that ozone (5%) is not decomposed by passing it through pyrex glass equipment at temperatures as high as 150° C., or by bubbling it through water. However, ozone passed into the vapors of 2-methyl-1-butene or 2-methyl-1-pentene, under reflux, completely reacted. By extracting the solution with water and treating the aqueous extract with dilute hydrogen peroxide, the presence of butanone and pentanone-2 were qualitatively established by the formation of their corresponding 2,4-dinitrophenylhydrazones. It thus appears that volatile olefins may be ozonated in their vapor state. However, good yields, isolation of desired products, and effective vapor phase equipment, along with investigations on ozone equilibrium and extent of ozone decomposition in the presence of organic vapors are important problems to be investigated.

B. Work Contemplated but Not Started:

Ozonization of Substituted Quinolines:

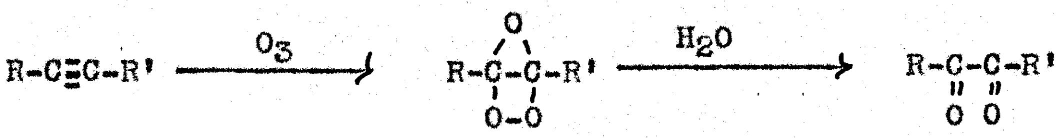
The preparation of substituted quinolinic acids might readily be accomplished by the ozone oxidation of quinoline with substituents in both the benzene and pyridine nucleus. An example would be the preparation of 6-fluoroquinolinic acid by the ozone oxidation of 2-fluoro-8-hydroxyquinoline.

Study of the Effect of Moisture on Ozone Oxidations:

It has been observed by this investigator and others that the presence of small amounts of water has varying effects upon ozonization rates. In some instances, the rate of reaction is considerably decreased, and in others, the ozonide is partially decomposed, directly yielding various oxidation products. Such solvents as acetic acid and ethyl acetate, which are miscible with water, show this phenomenon and would be the most desirable for future study.

Ozonization of Acetylene Derivatives:

Limited research has been done on the ozonization of acetylene derivatives. Ozone attacks the triple bond to form an ozonide, which, when cleaved, yields diketones, α-keto aldehydes, or the corresponding α-keto acids.



This appears to be a valuable and unexploited method of obtaining α-diketone compounds.

VII. SUMMARY

Quinolinic acid was prepared in 90-95% yields by the ozone oxidation of 8-hydroxyquinoline and the subsequent cleavage of the resulting diozonide with hydrogen peroxide, while cinchomeronic acid was prepared in 45% yields by similar treatment of isoquinoline. Quinoline produced a stable ozonide which was resistant to oxidative and reductive cleavage, yielding only tares.

A study was made of the effect of various substituents on the ozone oxidation of substituted quinolines. Quinoline derivatives bearing one or more substituents in the benzene ring added ozone less rapidly than quinoline itself, particularly if the substituents were electron-withdrawing in nature. All gave quinolinic acid as the only identifiable product, in poor yield if the substituents were electron-withdrawing, in good yield if they were electron-releasing.

The following compounds were prepared and ozonated in 6, 15, 65, and 44% yields, respectively: 6-nitroquinoline, 6-fluoroquinoline, 6-aminoquinoline, and 6-fluoro-8-aminoquinoline.

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PART II

THE PREPARATION OF FLUORINE-CONTAINING MEDICINALS

TABLE OF CONTENTS

I. INTRODUCTION

A. Chemotherapeutic Agents

1. Development of Chemotherapy: The use of chemical agents in the treatment of infectious diseases is known as chemotherapy. From the time Ehrlich first laid the foundations of modern chemotherapy, he emphasized the importance of attempting to determine the mechanism of action of chemotherapeutic agents. He believed that by thorough, planned research, specific drugs could be synthesized which would attack and kill specific organisms, and that eventually, through a systematic approach, the chemist could rid the world of all major infectious diseases.

The first chemotherapeutic agents were naturally-occurring products. In 1630 the use of cinchona bark was instituted in the treatment of malaria. Two centuries later, the alkaloid, quinine, the first specific drug to be used in an infectious disease, was isolated from the bark. Later, morphine was isolated from opium, and emetine from ipecac. The latter was first employed in India as an effective symptomatic treatment for certain types of dysentery.

In 1910, Ehrlich announced the preparation of arsphenamine[1], his 606th compound, developed as an anti-syphilitic drug. The importance of arsphenamine and subsequent drugs in the cure of syphilis cannot be overestimated. Not only was this discovery a triumph of years of systematic pharmacological research, but it represented the first bactericidal drug with a definite specificity for an invading pathogen.

In 1920, Young synthesized and showed the use of mercurochrome as an antiseptic agent. As Ehrlich had united arsenic to carbon in the preparation of arsphenamine, Young attached mercury to a dye molecule. It was hoped that this compound would serve as the great therapeutic sterilizing agent, "Magna Therapia Sterilisans", which Ehrlich had predicted would soon be synthesized. Ehrlich pleaded for a drug which would sterilize the blood when infected with streptococci or staphylococci, just as arsphenamine had killed the spirochetes.

In 1927, Dohme and co-workers developed the use of hexylresorcinol. It was shown that by the introduction of alkyl groups at position "4" in the resorcinol molecule, the germicidal value of the compound could be enhanced. Further, the germicidal capacity of the compound appeared to increase with the number of carbon atoms in the alkyl side chain. A maximum was obtained at six, and hence the use of hexylresorcinol.

The next significant advance in this field was in 1935, when Gerhard Domagk's[2] immortal paper appeared in a German clinical journal, regarding the use of certain sulfonated dyes in the treatment of streptococcal septicemias. He found that the dyes prontosil and neoprontosil were broken down in the body and excreted in the urine, partially as sulfanilamide. This substance thus made its advent into medicine. Sulfanilamide, a simple, comparatively non-toxic organic compound, heralded a new era in the treatment of infectious diseases. Rapidly there followed the syntheses of thousands of sulfanilamide derivatives, and today we have in clinical usage such important anti-infective drugs as sulfathiazole, sulfamerozine, and sulfaphthalidine.

Another important advance in the field of chemotherapy was the development of synthetic anti-malarial drugs. No substantial advance was made from this approach until 1926, when Schulemann and co-workers began their modification of the methylene blue molecule, and eventually succeeded in preparing Plasmoquine[3]. An extension of these studies led to the development of Atabrine[4] in 1930.

With the establishment in 1941 of a research program under the auspices of the Committee on Medical

Research of the Office of Scientific Research and Development, a systematic approach to the synthesis of antimalarials took place in the United States. Since 1941, more than 14,000 compounds have been screened for antimalarial activity by British and American investigators.[5] Of these compounds studied, at least two have established a place in therapy; they are Chloroquine and Paludrine.

2. Development of Antibiotics: Bacteriologists have recognized for many years that a growing culture of an organism may, under certain conditions, elaborate a substance which is inhibitory to a different strain of microorganisms. In modern terminology the word "antibiotic" has been employed to designate a substance, produced by or derived from living cells, which has a powerful lethal or inhibitory action on microorganisms, and is especially applicable to those substances produced by living bacteria, yeasts, molds, and other plants.

In recent years a number of systematic studies have been made to determine the distribution of antibiotic substances in nature. Antibiotics have been commonly found to be present in many natural forms of animal and plant associations, but their isolation and purification is difficult.

Alexander Fleming in 1928 observed a contamination of a culture plate of staphylococci by spores of a species of penicillium[6]. From this observation he suspected that the fungus elaborated a material antagonistic to the growth and development of the staphylococcus organism. Fleming demonstrated that the contaminating mold could be grown in special media and that the culture broth contained a potent antibacterial substance. The material was shown to be effective against a variety of gram-positive organisms and to be non-toxic to animals. Fleming gave the name penicillin to this antibiotic.[7, 8]

Since this discovery, many other promising antibiotics have been investigated and clinically tested. Streptomycin was discovered by Waksman[9] in 1943, and is active against gram-negative organisms. Chloromycetin was discovered in 1947 by Burkholder[10], and is active against Rocky Mountain spotted fever, rickettsia, typhus, and typhoid fever. Another important recent antibiotic is Aureomycin[11], which is effective against various viruses.

B. Physiological Agents

1. Curare-Type Compounds

a. Curariform Activity and Chemical Structure:

Curare has been known for many years to cause muscular paralysis when injected into frogs and mammals. This material had been brought from South America to Europe in small quantities by explorers, and was known to have been prepared by the natives in the form of aqueous extracts and concentrates for use as an arrow poison.

The physiological effect of curare has been found to have useful applications in surgery and in the treatment of spastic and other paralytic conditions. Bernard in 1844 first described the location of the physiological action of curare as being at the junctions of the nerves and muscles. The paralytic action of curare led to its early investigation in causing relaxation of muscles in such convulsive conditions as epilepsy, rabies, tetanus, strychnine poisoning, and various tics. The nonhomogeneity of the crude curare preparations made physiological investigation and clinical use difficult, with the result that a large number of synthetic and naturally-occurring organic compounds have been studied which have physiological effects similar to, although in practically all cases less intense than, the active materials present in the original South American curare.[12]

It is generally agreed that the curare action is one of prevention, in some manner, of the transfer of impulses from the nerve to the muscle at the myoneural junction. The most widely accepted theory for the mechanism of neuromuscular transmission is the acetylcholine theory, which states that an impulse from the nerve causes the formation of acetylcholine, which in turn causes stimulation of the muscle. The acetylcholine formed by each impulse is quickly hydrolyzed by cholinesterase, and the process, which takes place at the myoneural junction, is repeated for each impulse of the nerve. Rosenblueth and co-workers[13] postulated that there is a range of concentration of acetylcholine to which the muscle responds. Response by the muscle does not occur if the concentration is below the "threshold of excitation" or above the "upper paralytic boundary". This postulate explains why the injection of acetylcholine or drugs that are known to inhibit the action of cholinesterase cause curare-like paralysis, since the acetylcholine would be present in concentrations above the upper paralytic boundary. Because curare does not interfere with the liberation of acetylcholine and does not inhibit the action of cholinesterase, they believed that the action of curare was one of raising the threshold of excitation of the muscle. Thus, it is postulated that although the usual amount of acetylcholine is produced by the impulse from the nerve, it is not enough to cause response by the muscle.

The peripheral paralysis due to curare occurs in a definite order, so that the first signs of curare poisoning are dropping of the eyelids, drowsiness, loss of speech, and paralysis of the neck muscles. The extremities are then affected, followed by the muscles of the diaphragm; finally, death occurs from respiratory failure. A compound which produces a true curariform action has no effect on the central nervous system or the heart. Reflexes are diminished but not abolished, and a paralyzed muscle returns to its normal state without showing any harmful effects. That death occurs from respiratory failure before other toxic manifestations are noted has been shown by giving dogs up to fifty times the ordinary lethal dose of a curare preparation, without fatality, by maintaining artificial respiration.

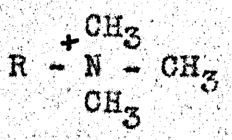
Three general types of curare activity attributed to the action of quaternary ammonium compounds are curare action, muscarinic action, and nicotinic action.

A muscarinic action is one of direct stimulation of smooth muscles, which is manifest in mammals by slowing of the heartbeat, depression of the blood pressure, vasodilation, miosis, bronchial constriction, salivation, and sweating. Renshaw and Hunt[14] used as a criterion for muscarinic activity the production of a fall in blood pressure, which was prevented by atropine, the latter being a specific antagonist to muscarinic activity.

A nicotinic action consists of a primary, transient stimulation and a secondary, more persistent depression of all sympathetic and parasympathetic ganglia. Thus, the first signs of a nicotinic action are a rise in blood pressure due to vasomotor paralysis. In the stage of paralysis, nicotine thus manifests a curare-like paralysis which largely explains the fact that death from nicotine is due to respiratory failure.

Since the active curare alkaloids were quaternary salts, many quaternary compounds have been investigated, and it has been found that quaternary ammonium, sulfonium, phosphonium, arsonium and stibonium salts all possess curare activity. Although all of these onium ions exhibit curariform activity to some extent, the quaternary ammonium compounds— the alkylammonium, the arylalkylammonium, the heterocyclic ammonium, and the alkaloids— are most effective.

In general, all of the R_4N^+ tetralkylammonium salts possess curare activity. Tetramethyl- and



$$R - \overset{+}{N}(CH_3)_2 - CH_3$$

trimethylammonium salts have very pronounced curare actions, a maximum effectiveness in the trimethylalkyl series being reached with the butyl and amyl derivatives[15]. Polymethylene bis quaternary ammonium salts possess activity, especially when $R = CH_3$ and

$$R_3 - \overset{+}{N} - (CH_2) - \overset{+}{N} - R_3$$

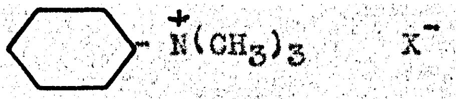
n = 2, as do derivatives of choline and neurine[16].

$$HO\text{-}CH_2CH_2\overset{+}{N}(CH_3)_3 \qquad CH_2 = CH\overset{+}{N}(CH_3)_3$$

Choline Neurine

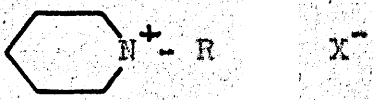
Unsaturated compounds of the neurine type in general possess more effective physiological properties, but are usually more toxic than the corresponding saturated compounds.

Aryltrialkylammonium compounds exhibit



muscarinic, nicotinic, and weak curare actions. The replacement of an alkyl group on a quaternary nitrogen with an aryl group reduces the curare activity.

The alkylpyridinium salts possess weak curare activity, in some cases marked muscarinic



activity, and in general, no nicotinic activity. The benzyl pyridinium salt is the most effective of the pyridine derivatives. The ethyl and propylpyridinium salts are less effective than the methyl derivatives. The isoamyl and cetyl derivatives have an action comparable to the methyl derivatives. Reduction of the ring to the corresponding piperidinium compounds usually increases the curare action and reduces the muscarinic and nicotinic actions and the toxicity.[17]

Quinolinium and isoquinolinium compounds[18] show curare activity. Increasing the length of the alkyl group usually increases the intensity of the activity but also increases the toxicity.

The active constituents of South American curare are quaternary alkaloids. The tertiary alkaloids have a very weak or no paralyzing action, but become very effective upon conversion to the quaternary bases. Active curare compounds have been prepared by forming the quaternary salts of Erythrina alkaloid, quinine, and cinchonine.

b. α-Glycerol Ethers: In the past little attention has been paid to the pharmacological properties of α-substituted ethers of glycerol. In 1910 Gilbert and Descomps[19] investigated 3-phenoxypropan-1,2-diol and observed that it caused transient paralysis in guinea pigs and rabbits and a sharp but transient fall of body temperature in dogs. The French authors also reported the results of preliminary clinical trials and recommended the substance as an antipyretic and analgesic. It was commercially available under the name of "Antodyne"[20]. Berger and Bradley[21,22] investigated the pharmacological properties of a large number of simple monoethers of glycerol and found that certain of these compounds possessed a peculiar central depressant action. They suggested that Myanesin, 3-(2'-methyl-phenoxy) propan-1,2-diol, the most suitable and the safest compound of the series, may be useful in the treatment of spastic and hyperkinetic states and for the production of muscular relaxation during anaesthesia.

The duration of paralysis is relatively short, but repeated doses show no cumulative effects, and tolerance is not built up. In therapeutically effective doses, there has been no evidence of toxic effects on any organ of the body. Myanesin has well-marked advantages over curare in certain applications, having a much greater margin of safety and bringing about relaxation without distress. It is much more effective with barbiturate anaesthesia than curare, apparently enhancing the action of the barbiturates.

Berger[23] reports that many substances of the structure $R-O-CH_2-CHOH-CH_2OH$ produced transient muscular relaxation and paralysis. These effects were due to a depressant action on the central nervous system and particularly on the spinal cord. The paralyzing action was strongest when R was a benzene nucleus substituted in the ortho position with a small alkyl or alkoxy group or chlorine. Compounds with these radicals in meta or para position were less active than the ortho isomers. The presence of a hydroxy, amino, amido, ester or hydroxyalkyl group or multiple substitution in the ring with alkyls, halogens, or both, decreased paralyzing activity. When R was an aliphatic radical, straight chain alkyls contributed more to the paralyzing activity than the branched chain isomers or unsaturated radicals. The n-amyl ether was the most potent compound of the aliphatic series. Methyl substitution on the C_2 atom of the glyceryl side chain did not materially alter paralyzing activity, but substitution of the C_1 atom decreased activity. Compounds possessing the structure $R-S-CH_2-CHOH-CH_2OH$ or $R-SO_2-CH_2-CHOH-CH_2OH$ also have paralyzing activity, but were more toxic than the oxygen ethers. Compounds of the structure aryl-$O-CH_2-CHOH-CH_2OH$ and aryl-$S-CH_2-CHOH-CH_2OH$ increased the threshold to electrically-induced convulsions. There was no simple relation between the anticonvulsant and paralyzing activity of the compounds, and the anticonvulsant action could not be significantly altered by alkyl or alkoxy substitution in the nucleus.

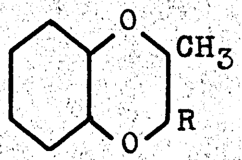
2. Sympatholytic Agents and Activity

Agents which stimulate the sympathetic division of the autonomic nervous system are quite numerous. In addition to the hormone epinephrine, the most important of this group, there is a large number of substances similar to it in structure, which mimic its action on the sympathetic nervous system. These substances are referred to collectively as the sympathomimetic amines. To this class of substances belong the alkaloids ephedrine, Neo-synephrine, and amphetamine.

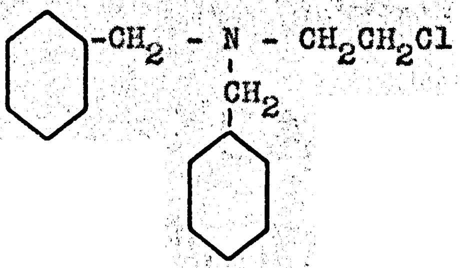
The sympatholytic drugs which successfully block or depress the impulse of sympathetic nerves are few.[24] Their use is fraught with many toxic side-reactions and consequently their therapeutic application is limited. A sympatholytic drug with marked specificity and a relatively low toxicity is not available at present.

A sympatholytic drug antagonizes epinephrine, similar to the antagonism between atropine and acetylcholine. It acts as a depressant by slowing the rate of the heart through depression of the cardiac accelerator and by producing extensive peripheral vasodilation and increasing the tone of the gastro-intestinal muscle.

Until recently the closest approach to such a drug has been the two alkaloids, ergotamine and ergotoxine. Fourneau and his associates[25, 26] have synthesized a number of dioxane derivatives which appear to exhibit a direct specificity in antagonizing the action of epinephrine. These compounds possess the following typical structure:



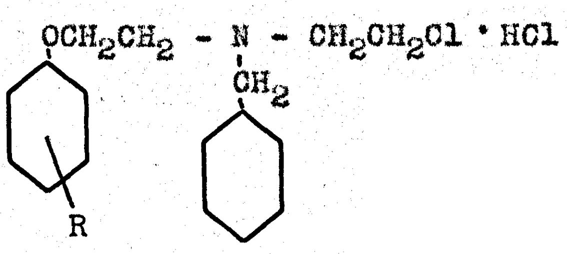
One of the most promising of the newer synthetic sympatholytic agents is Dibenamine, (N,N-dibenzyl-β-chloroethylamine).



Dibenamine has been studied pharmacologically and clinically by Goodman and his associates[27]. The free base is an oily liquid but the hydrochloride is a white crystalline compound slightly soluble in water. The compound produces an epinephrine reversal in blood pressure, presenting a response similar to ergotamine.

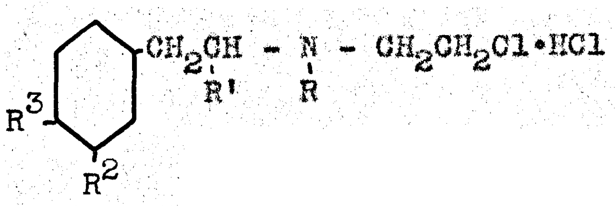
It was shown that Dibenamine does not destroy epinephrine chemically, either in *vitro* or in *vivo*, and, as it blocked the direct sympathetic stimulation of epinephrine, Nickerson[27] concluded that it probably acts on the effector cells in the organs. However, Dibenamine produces local tissue damage and also causes central nervous system stimulation.

Following the important discovery of Dibenamine, a series of N-[2-(2-biphenyloxy)ethyl]-N-(2-chloroethyl) alkylamines[28] and a related compound, N-[2-(*o*-benzylphenoxy)ethyl]-N-(2-chloroethyl) ethylamine[29] were synthesized and reported to be epinephrine antagonists. These compounds contain either phenyl or benzyl groups in ortho positions to the phenoxyethyl group. Gump and Nikawitz[30] synthesized a series of N-(2-chloroethyl)-N-(2-phenoxyethyl) amines having alkyl, methoxy and halogens as ring substituents, in an attempt to find substances of higher potency and to acquire further knowledge on the relationship between structure and activity. The least toxic and at the same time the most potent sympatholytic agent was:



where R was a methyl, ethyl or isopropyl group in the ortho position. Similar compounds in which the benzyl group was replaced by an ethyl or 2-phenoxyethyl were less effective.

Kerwin, Herdegen, Heisler and Ullyot[31] synthesized a series of N,N-disubstituted-β-chloroethylamines of the following type:



where R = alkyl groups; R' = methyl, phenyl or benzyl; and R^2 and R^3 = hydrogen, hydroxyl or methoxy. These amines when administered intravenously to a cat at low dosage levels completely blocked the excitatory effects of as much as 1 mg./kg. of injected epinephrine.

C. Concepts Involved in the Synthesis of Chemotherapeutic and Physiological Agents

1. Concept of Metabolite Antagonism:

The concept that substances chemically related to a metabolite may interfere with the normal function of that metabolite in living cells has attracted widespread interest.[32] This concept frequently provides a unique starting point for the synthesis of biologically active compounds and the study of the relation between chemical structure and activity. The stimulus for many investigations utilizing this concept came from the discovery of the striking relationship between p-aminobenzoic acid and sulfanilamide-type compounds. However, not all important antagonists are structurally related to the affected metabolite and the value of specific antagonists must be recognized.

Broadly, an essential metabolite may be regarded as any substance involved in the chemical processes by which living cells are produced and maintained, regardless of their biological function. Thus, any substance made available to the living cell, which is similar in size, structure, and electronic configuration to the original metabolite, may be readily accepted in place of the genuine metabolite. Further, the spurious metabolite attenuates or kills the cells which attempt to use it.

With this theory as the basis, numerous metabolite antagonists have been developed in which the antagonist is a slight structural modification of the original metabolite. Some examples of such antagonists are the sulfa drugs for p-aminobenzoic acid, pyridine-3-sulfonic acid as an antagonist of nicotinic acid[33], phenylpantathenone as an antagonist of pantothenic acid[34], and pyrithiamin as an antagonist of thiamin[35].

It is necessary to remember, in synthesizing a metabolite antagonist, that essential vitamin deficiency might result in man as well as in the specific organism one desires to destroy. Thus it is apparent that the analogues of the vitamins essential to man cannot be employed as chemotherapeutic agents if they harm the host more than the pathogenic organism. In cases where their structure has been elucidated, growth factors not essential to man but essential to the organism provide a feasible avenue of attack.

2. The Concept of Isosterism

The concept of isosterism was first introduced by Langmuir[36] in 1919. Since that time the original restricted definition has undergone considerable modification and extension.

Langmuir originally proposed that molecules or groups which have the same number of atoms, and the same total number of electrons arranged in the same manner, be described as "isosteric". He called attention to the fact that when isosteres are also isoelectric (when they have the same total charge), they then possess strikingly similar physical properties. Classic examples of pairs of isosteres showing extraordinarily close agreement in physical constants are carbon monoxide and nitrogen, and carbon dioxide and nitrous oxide.[38] These examples,

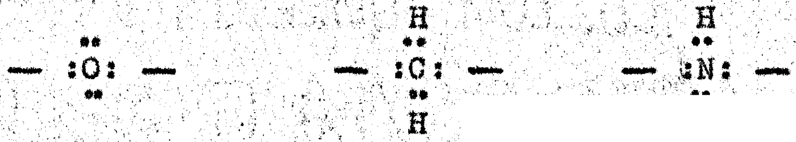
$$:\mathrm{N}:::\mathrm{N}: \qquad :\mathrm{C}:::\mathrm{O}: \qquad :\ddot{\mathrm{O}}::\mathrm{C}::\ddot{\mathrm{O}}: \qquad :\ddot{\mathrm{N}}::\mathrm{N}::\ddot{\mathrm{O}}:$$

however, fail to consider resonance structures, which, in the case of the carbon dioxide and the nitrous oxide, are not equivalent.

Grimm[39] in 1929 made a rather unsuccessful attempt to explain isomorphism, but in doing so, broadened the concept of isosterism to include molecules or groups possessing the same number of valence electrons, whether or not the same number of atoms were involved. According to Grimm's definition, groups of the following types are classed as isosteric: fluoride, hydroxyl, amino, and methyl;

$$-\,:\overset{\cdot\cdot}{\underset{\cdot\cdot}{F}}: \qquad -\,:\overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}:H \qquad -\,:\overset{\overset{H}{\cdot\cdot}}{\underset{\cdot\cdot}{N}}:H \qquad -\,:\overset{\overset{H}{\cdot\cdot}}{\underset{\underset{H}{\cdot\cdot}}{C}}:H$$

oxide, methylene, and imide;

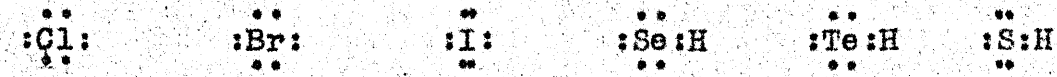


$$-\,:\overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}:\,- \qquad -\,:\overset{\overset{H}{\cdot\cdot}}{\underset{\underset{H}{\cdot\cdot}}{C}}:\,- \qquad -\,:\overset{\overset{H}{\cdot\cdot}}{\underset{\cdot\cdot}{N}}:\,-$$

and acetylide and cyanide.

- :C:::C:H   - :C:::N:

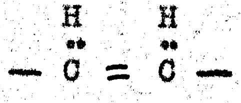
However, by Grimm's definition such groups as chloride, bromide, iodide, thiol, etc.,



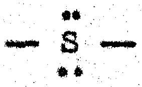
$$:\overset{\cdot\cdot}{\underset{\cdot\cdot}{Cl}}: \qquad :\overset{\cdot\cdot}{\underset{\cdot\cdot}{Br}}: \qquad :\overset{\cdot\cdot}{\underset{\cdot\cdot}{I}}: \qquad :\overset{\cdot\cdot}{\underset{\cdot\cdot}{Se}}:H \qquad :\overset{\cdot\cdot}{\underset{\cdot\cdot}{Te}}:H \qquad :\overset{\cdot\cdot}{\underset{\cdot\cdot}{S}}:H$$

are isosteric with group I, as they all contain the same number of valence electrons.

Erlenmeyer[40] pointed out that various dyes containing -O- or its isosteric $-CH_2-$ linkage between aromatic rings exhibited almost identical absorption spectra. He also proposed[41], in what is perhaps his major contribution to the concept of isosterism, that the aromatic $-CH = CH-$ group and the ring sulfur atom are isosteric. Erlenmeyer arrived at this conclusion by arguing that only the boundary electrons (the



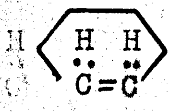
$$-\overset{H}{\overset{\cdot\cdot}{C}}=\overset{H}{\overset{\cdot\cdot}{C}}-$$

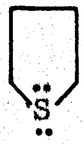


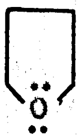
$$-\underset{\cdot\cdot}{\overset{\cdot\cdot}{S}}-$$

outer electrons of the group), should be counted in determining isosterism. Thus, in this case, the two electron pairs shared by the carbon atoms are not to be counted, as they are considered to be within the group, or "pseudoatoms".

A broad definition such as this results in compounds such as benzene, thiophene, furan and pyrrole being isosteric, and although the physical constants of benzene and thiophene are very similar, those of furan and pyrrole differ widely. Such







differences may be accounted for by the fact that the degree of resonance stabilization of the thiophene molecule, like that of benzene, is significantly larger than that for furan[42], while in the case of pyrrole, the molecules can associate through hydrogen bonding involving the amino-hydrogen atom.

It is apparent that the broad definition of isosterism, which classified atoms or groups containing the same number of boundary electrons as isosteric, does not necessarily provide a valid basis for the prediction of similarities in physical and chemical properties. One must take into account such factors as resonance possibilities, opportunities for hydrogen bonding, and size. Without exception, the only cases in which isosteric groups do actually confer similar properties to substances are those in which the groups involved differ little in weight.

Erlenmeyer[41] found that even in the exceedingly specific antigenantibody reactions, certain corresponding derivatives of benzene and thiophene proved to be indistinguishable.

A classic illustration of the use of isosterism is that of isosteric derivatives of sulfapyridine, sulfadiazine and sulfathiazole[43]. The replacement of the benzene by the thiophene ring in cocaine produced a compound closely resembling cocaine in its physiological effect[44], while the alkylamine ester of p-fluorobenzoic acid has similar anaesthetic properties to those of the corresponding derivatives of p-hydroxybenzoic acid[45].

It is apparent, therefore, that the principle of isosterism can be used with success to predict similarities only when applied with great caution and after careful consideration of all pertinent factors. As applied to certain specific groups whose similar effects have been well established, the concept of isosterism is playing an important role in suggesting the possibilities of new physiologically active agents which differ from compounds of tested value only in the substitution of one such isosteric group by another.

II. EXTENT OF PRESENT INVESTIGATION

The extent of the present investigation includes the attempted synthesis of fluorine isosteres of the essential amino acids leucine, isoleucine, norleucine, tyrosine, and serine, and the vitamins pyridoxine (Vitamin B_6) and pantothenic acid. As discussed in the previous section on the concept of isosterism, the fluorine atom is isosteric with the hydroxyl and the amino groups, and therefore the replacement of the amino groups in the essential amino acids and the hydroxyl groups of the above-mentioned vitamins should result in compounds of interesting pharmacological properties and physiological activity.

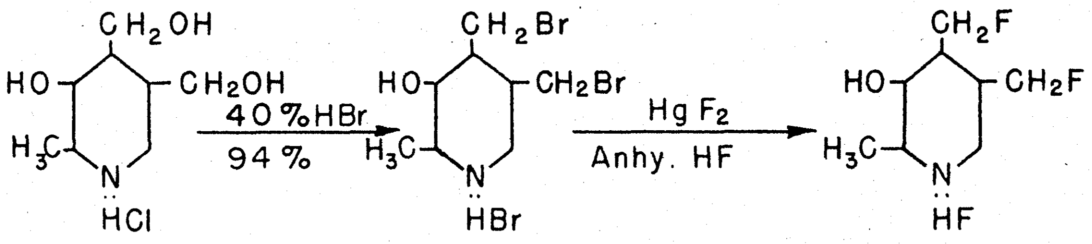
It is also postulated that the replacement of these isosteric groups with a fluorine atom, in compounds known to be essential metabolites or vitamins, might produce a reversal of the activity characterizing the parent compound, producing a metabolite antagonist or what is commonly classified as an anti-amino acid or anti-vitamin. It is also hoped that desirable changes in the physiological activity of such compounds will not be accompanied by an excessive increase in the toxicity.

A second approach to the study of the effect produced by the fluorine atom in various physiologically active compounds is the introduction of a fluorine atom for a hydrogen atom. The comparatively small atomic radius of the fluorine atom is of the order of that of the hydrogen atom, and, like hydrogen, it requires only one electron to complete its valence shell. Thus we have undertaken the synthesis and pharmacological testing of a series of central depressant and sympatholytic agents in which fluorine has been substituted for the hydrogen, and trifluoromethyl for the methyl group in the ortho, meta, and para positions of the aromatic ring. The central depressant agent chosen for this investigation was 3-(2-methylphenoxy)-propan-1,2-diol (Myanesin), and the sympatholytic agent N-[β-(2-methylphenoxy)-isopropyl]-N-benzyl-β-chloroethylamine hydrochloride. By introducing a fluorine atom or a trifluoromethyl group into these compounds, we hope to enhance their physiological activity without excessively increasing their toxicity.

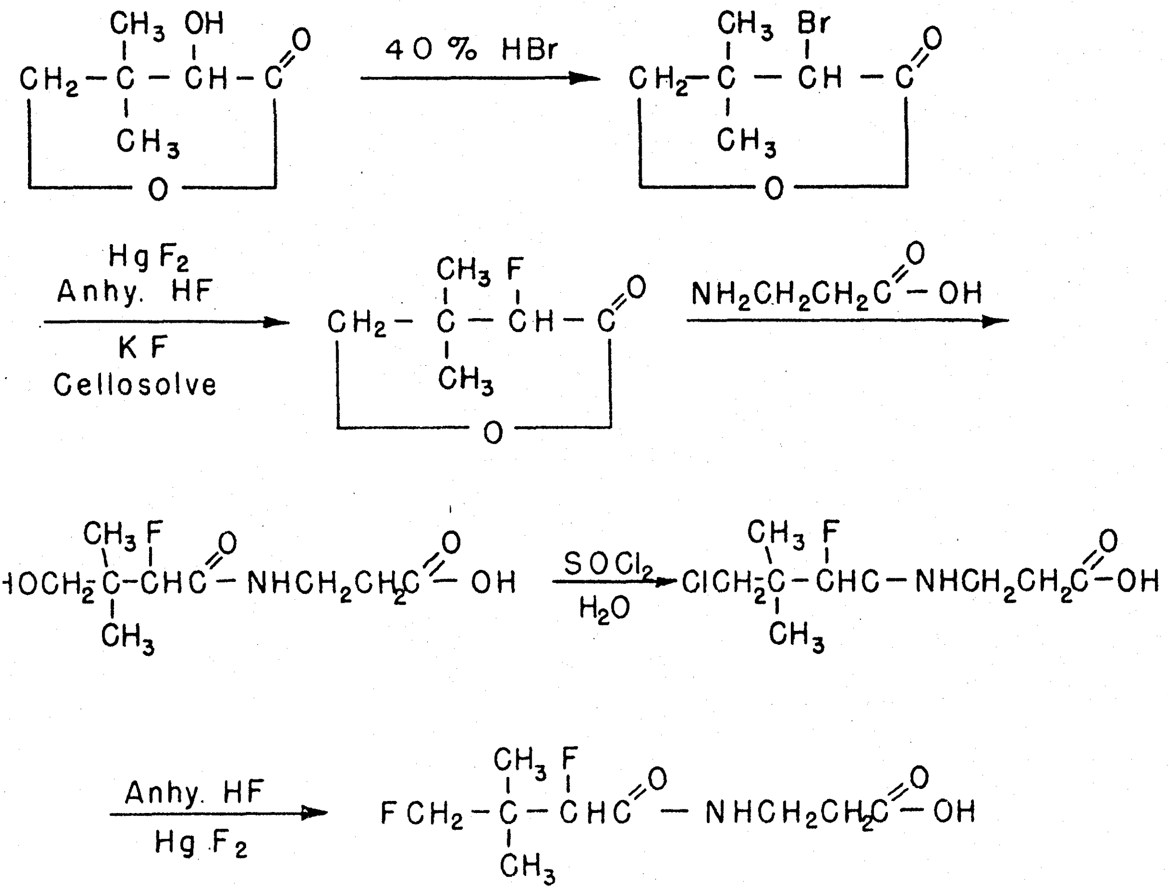
EXPERIMENTAL

I. - Attempted Synthesis of Fluoro-Antivitamins

Fluoro Analog of Pyridoxin - Vitamin B6:

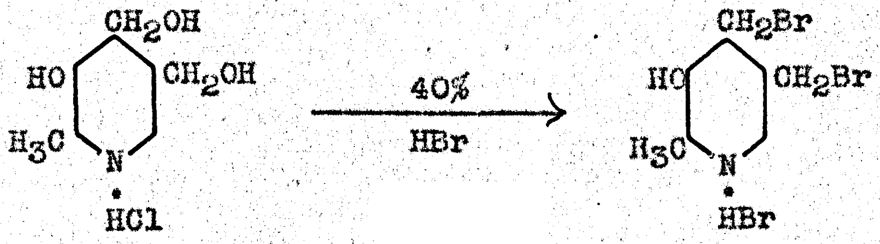


Fluoro Analog of Pantothenic Acid:



III. EXPERIMENTAL

Preparation of Dibromopyridoxine Hydrobromide[46,47]:

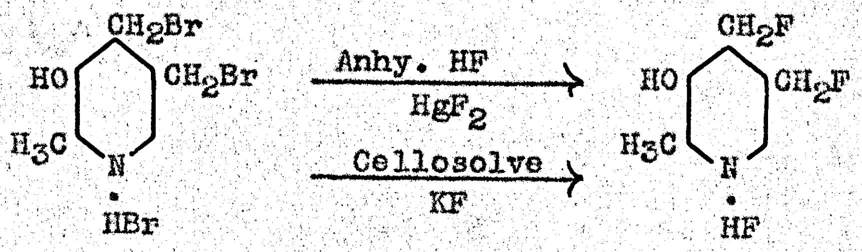


205 g. (1.0 mole)	376 g. (1.0 mole)
20 g. (0.097 mole)	34 g. (0.091 mole)

$$\% \text{ Yield} = \frac{0.091}{0.097} = 94\%$$

A flask charged with 20 g. (0.097 mole) of 2-methyl-3-hydroxy-4,5-di-(hydroxymethyl)-pyridine hydrochloride (Pyridoxine Hydrochloride, Vitamin B_6) and 500 ml. of 40% hydrobromic acid was refluxed for two hours. The solution was cooled, the crystals filtered and washed thoroughly with water, acetone, and then ether. The yield of 2-methyl-3-hydroxy-4,5-di-(bromomethyl)-pyridine hydrobromide, melting at 223° (partial decomposition 217°) was 34 g. (94%).

Attempted Preparation of Difluoropyridoxine Hydrofluoride[48]:



376 g. (1.0 mole)

5 g. (0.0133 mole)

No Yield

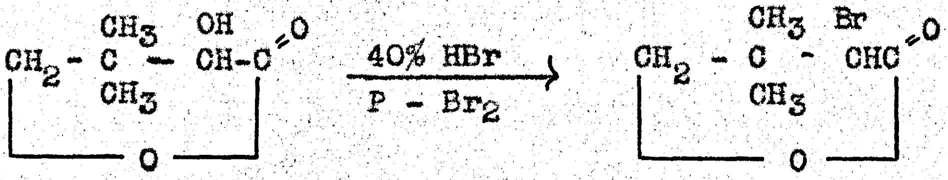
Method A:

To 5.0 g. (0.0133 mole) of 2-methyl-3-hydroxy-4,5-di-(bromomethyl)-pyridine hydrobromide dissolved in 30 ml. of liquid anhydrous hydrogen fluoride maintained at 0° C. in a metal beaker, 4.3 g. (0.02 mole) of mercuric oxide was added, with vigorous stirring. The red mercuric oxide gradually turned into white mercuric bromide, and after thirty minutes the white solid was separated, the hydrogen fluoride evaporated, and attempts made to purify the resulting material by recrystallization from anhydrous acetone, alcohol, etc. Only tarry materials were obtained.

Method B:

Dibromo-pyridoxine hydrobromide (5.0 g., 0.0133 mole) was dissolved in 50 ml. of freshly-distilled anhydrous cellosolve, heated to 135°, and 10 g. (0.042 mole) of mercuric fluoride added, with vigorous stirring. The solution turned a dark brown. The temperature was lowered to 60° and the solution agitated for three hours. The salt and solvent were removed, and only a resinous material, resistant to crystallization and purification, was obtained.

Attempted Preparation of α-bromo-β,β-dimethyl -γ-butyrolactone:



130 g. (1.0 mole) 193 g. (1.0 mole)

5 g. (0.0384 mole)

No Yield

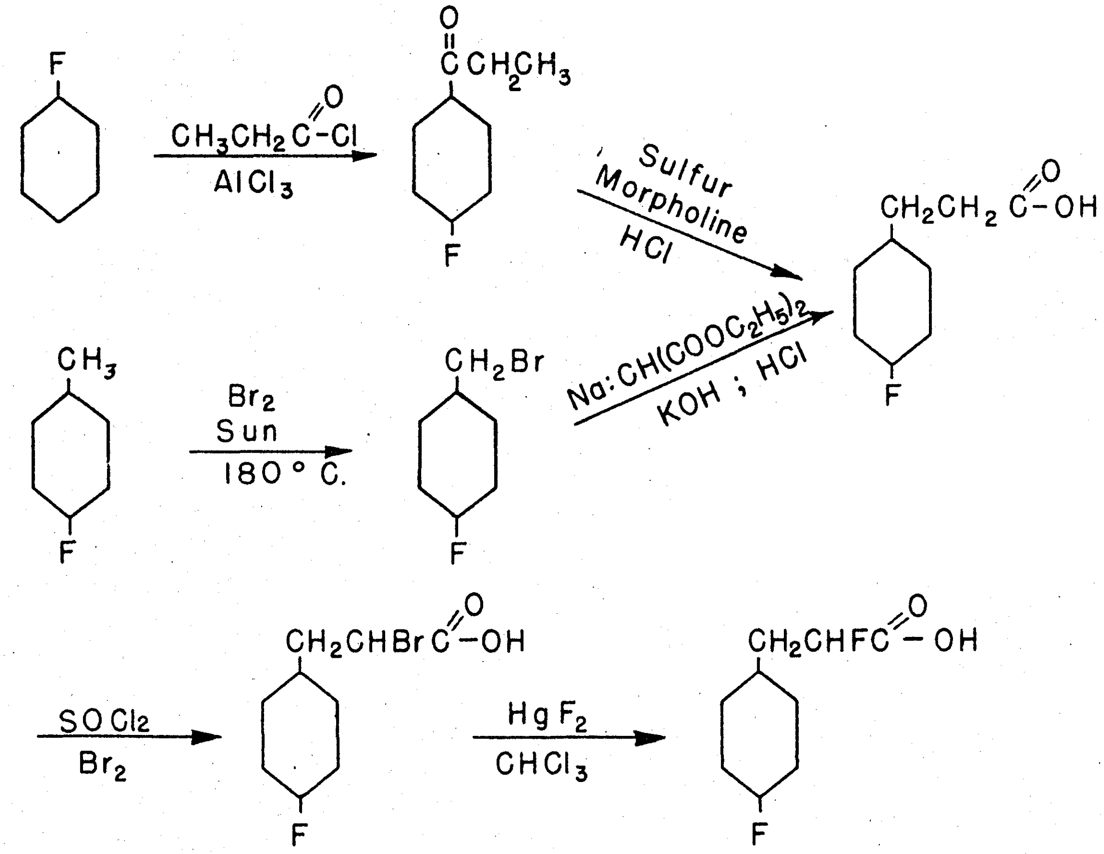
Method A:

α-hydroxy-β,β-dimethyl-γ-butyrolactone 5.0 g., 0.0384 mole), and 25 ml. of 40% hydrobromic acid were refluxed for three hours. The excess hydrobromic acid was removed under vacuum, the oil washed with water and ether extracted, the ether dried and removed by distillation. Attempts were made to purify

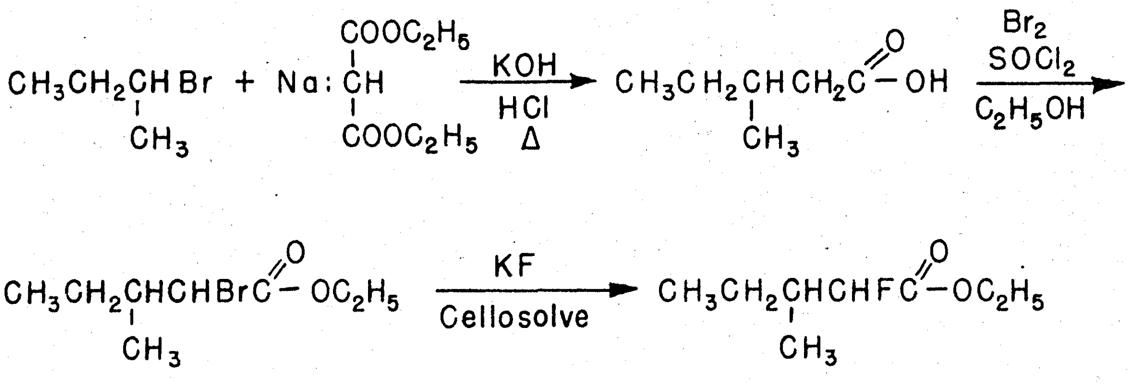
EXPERIMENTAL

II - Attempted Synthesis of Fluoro Analogs of Two Essential Amino Acids on their Esters

Fluoro Analog of Tyrosine:



Fluoro Analog of Isoleucine:



$$\underset{\displaystyle CH_3}{CH_3CH_2\overset{}{CH}Br} + Na:\underset{\displaystyle COOC_2H_5}{\overset{\displaystyle COOC_2H_5}{CH}} \xrightarrow[HCl\ \Delta]{KOH} \underset{\displaystyle CH_3}{CH_3CH_2CHCH_2}\overset{O}{\overset{\|}{C}}-OH \xrightarrow[C_2H_5OH]{Br_2\ SOCl_2}$$

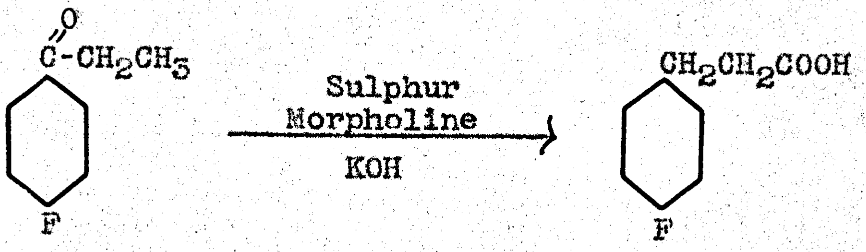
$$\underset{\displaystyle CH_3}{CH_3CH_2CHCHBr}\overset{O}{\overset{\|}{C}}-OC_2H_5 \xrightarrow[Cellosolve]{KF} \underset{\displaystyle CH_3}{CH_3CH_2CHCHF}\overset{O}{\overset{\|}{C}}-OC_2H_5$$

the resulting oil by crystallization or molecular distillation. All attempts failed to yield pure α-bromo-β,β-dimethyl-γ-butyrolactone.

Method B:

Similar quantities of the α-hydroxy-lactone, excess bromine, and red phosphorus (or PBr_3) were refluxed overnight. The excess bromine was removed, the oil washed with a sodium bisulfite solution, and then treated as described in the previous procedure. All attempts failed to yield pure α-bromo-β,β-dimethyl-γ-butyrolactone.

Preparation of β-(p-fluorophenyl)-propionic acid[49,50]:



152 g. (1.0 mole)	168 g. (1.0 mole)
74 g. (0.487 mole)	46 g. (0.273 mole)

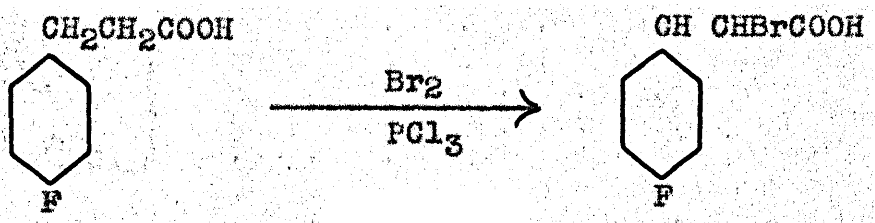
$$\% \text{ Yield} = \frac{0.273}{0.487} = 56\%$$

β-(p-fluorophenyl)-propionic acid was prepared from p-fluorophenyl ethyl ketone, using the "Willgerodt" reaction[49].

A mixture of 74.0 g. (0.487 mole) of p-fluorophenyl ethyl ketone, 26.0 g. (0.75 mole) of sulfur, and 65.0 g. (0.75 mole) of morpholine was refluxed at 130° C. for thirty hours. Hydrogen sulfide was liberated and a black solution resulted. The intermediate thioamide was hydrolyzed directly by the addition of 200 ml. of ethanol, 50 ml. of water, and 100 g. of potassium hydroxide, refluxing for six hours, and then evaporation to dryness. The resulting solid was dissolved in water, acidified, the sulfur removed by filtration, and the dark oil extracted with ether. The ether was dried over calcium sulfate, removed under vacuum, and the oil fractionated at 140-142° (2 mm.) to yield 46 g. (56%) of β-(p-fluorophenyl)-propionic acid, which, upon cooling, gave a solid melting at 89-90° C.

Anal. Calcd. for $C_9H_9O_2F$: C, 64.3; H, 5.4. Found: C, 64.6; H, 5.3.

Preparation of α-Bromo-β-(p-fluorophenyl)-propionic acid:



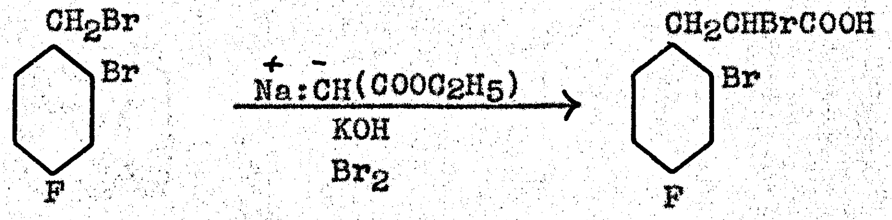
168 g. (1.0 mole)	247 g. (1.0 mole)
36 g. (0.214 mole)	47 g. (0.191 mole)

$$\% \text{ Yield} = \frac{0.191}{0.214} = 89\%$$

β-(p-fluorophenyl)-propionic acid (36 g., 0.214 mole), 40 g. (0.25 mole) of bromine, and 2 ml. of phosphorus trichloride were refluxed together overnight. The resulting oil was dissolved in ether, washed with water, treated with charcoal, and dried over calcium sulfate. The ether was removed under vacuum, and the solids recrystallized from Skelly-solve "B". The yield of crude material was 47 g. (89%).

Anal. Calcd. for $C_9H_8O_2FBr$: C, 43.8; H, 3.3.

Preparation of α-Bromo-β-(2-bromo-4-fluorophenyl) propionic acid:



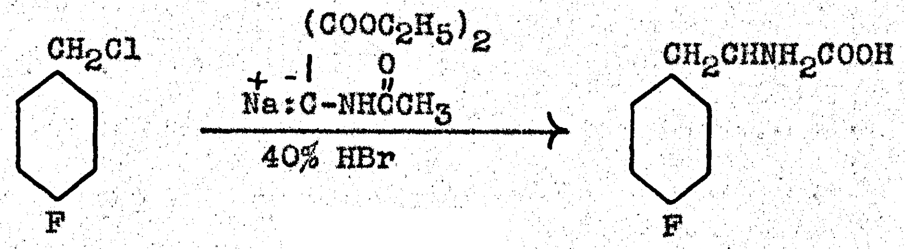
268 g. (1.0 mole)	326 g. (1.0 mole)
18.5 g. (0.0685 mole)	8.2 g. (0.0246 mole)

$$\% \text{ Yield} = \frac{0.0246}{0.0685} = 36\%$$

To 50 ml. of absolute alcohol containing 11.0 g. (0.0685 mole) of ethyl malonate and 1.57 g. (0.0685 mole) of sodium was added dropwise 18.5 g. (0.0685 mole) of 2-bromo-4-fluorobenzyl bromide. The mixture was refluxed for six hours, the sodium bromide removed by filtration, the alcohol distilled off under vacuum, and the resulting oil added dropwise to a hot solution of 100 ml. of water and 15 g. of potassium hydroxide and heated for an additional three hours. This solution was evaporated to dryness, then dissolved in 100 ml. of water, cooled to 0°, and acidified with excess hydrochloric acid while the temperature was maintained at 0° C. The acidic solution was ether extracted, 11 g. (0.0685 mole) of bromine was added dropwise to the ethereal solution, the mixture refluxed for three hours, the ether removed, and the resulting oil decarboxylated at 140° for two hours. The resulting material solidified upon cooling, and repeated recrystallizations from Skellysolve "B" yielded 8.2 g. (36%) of a white solid, melting at 174-175° C.

Anal. Calcd. for $C_9H_7O_2FBr_2$: C, 33.2; H, 2.2. Found: C, 33.6; H, 2.3.

Preparation of β-(p-fluorophenyl) alanine[51,52]:

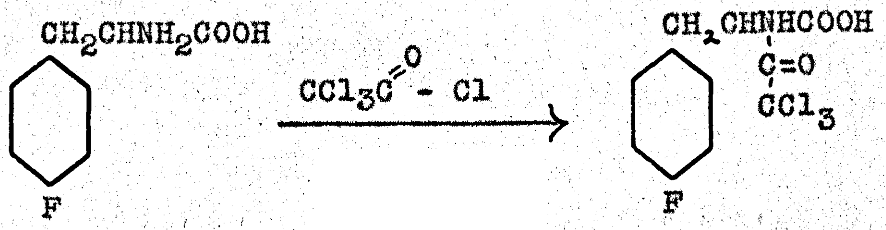


144 g. (1.0 mole)	183 g. (1.0 mole)
10 g. (0.70 mole)	6.6 g. (0.36 mole)

$$\% \text{ Yield} = \frac{0.36}{0.70} = 51.5\%$$

In a 1 l. three-necked flask supporting a stirrer, dropping funnel, and condenser, 15.0 g. (0.069 mole) of diethyl acetamidomalonate was added to 150 ml. of absolute alcohol and 1.59 g. (0.069 mole) of sodium. To the resulting clear solution 10 g. (0.70 mole) of p-fluorobenzylchloride was added dropwise, and the mixture was refluxed for six hours. The solution was filtered, the alcohol removed under vacuum, and the remaining solids refluxed with 65 ml. of 40% hydrobromic acid for nine hours. The hot acid solution was treated with decolorizing charcoal, cooled, and the pH adjusted to 6 with ammonium hydroxide. Upon chilling overnight, 6.6 g. (51.5%) of β-(p-fluorophenyl) alanine, decomposing at 261° (Lit. 263.5°)[52] was obtained.

Preparation of β-(p-fluorophenyl)-N-trichloroacetyl-alanine:



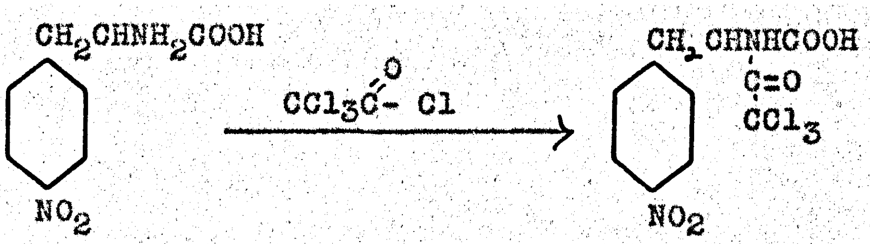
183 g. (1.0 mole)	328 g. (1.0 mole)
3 g. (0.0165 mole)	2.7 g. (0.0083 mole)

$$\% \text{ Yield} = \frac{0.0083}{0.0165} = 50.5\%$$

β-(p-fluorophenyl) alanine (3.0 g., 0.0165 mole) and 20 ml. of trichloroacetyl chloride were refluxed together for four hours. The excess trichloroacetyl chloride was removed under vacuum, and the resulting solids were dissolved in cold dilute sodium hydroxide. The basic solution was acidified, the solids filtered, washed, and dried under vacuum to yield 2.7 g. (50.5%) of impure β-(*p*-fluorophenyl)-N-trichloroacetyl-alanine, melting at 229-230°.

Anal. Calcd. for $C_{11}H_9O_3NFCl_3$: C, 40.2; H, 2.8. Found: C, 45.0; H, 2.6.

Preparation of β-(*p*-nitrophenyl)-N-trichloroacetyl-alanine:



209 g. (1.0 mole)	353 g. (1.0 mole)
3.0 g. (0.014 mole)	2.2 g. (0.0062 mole)

$$\% \text{ Yield} = \frac{0.0062}{0.014} = 43\%$$

β-(*p*-nitrophenyl)-N-trichloroacetyl-alanine was prepared from β-(*p*-nitrophenyl) alanine as described in the previous section. The yield of impure material melting at 245-246° was 2.2 g. (43%).

Anal. Calcd. for $C_{11}H_9O_5N_2Cl_2$: C, 37.20; H, 2.56; N, 7.90. Found: C, 39.48; H, 2.67; N, 9.92.

Preparation of Ethyl α-Bromocaproate[53]:

$$CH_3CH_2CH_2CH_2CH_2COOH \xrightarrow[\substack{Br_2 \\ C_2H_5OH}]{SOCl_2} CH_3CH_2CH_2CH_2CHBrCOOC_2H_5$$

130 g. (1.0 mole)	224 g. (1.0 mole)
232 g. (2.0 moles)	403 g. (1.80 moles)

$$\% \text{ Yield} = \frac{1.80}{2.00} = 90\%$$

A mixture of 200 ml. of thionyl chloride and 232 g. (2.0 moles) of caproic acid was refluxed for one hour; then 330 g. (2.06 moles) of bromine was added dropwise. The mixture was refluxed overnight and 200 ml. of absolute alcohol added dropwise. The excess solvents were removed and the resulting oil was distilled at 200-205° (736 mm.) to yield 403 g. (90%) of ethyl-α-bromocaproate.

Attempted Preparation of Ethyl-α-Fluorocaproate:

$$CH_3CH_2CH_2CH_2CHBrCOOC_2H_5 \longrightarrow CH_3CH_2CH_2CH_2CHFCOOC_2H_5$$

224 g. (1.0 mole) 162 g. (1.0 mole)

No Yield

Method A:

In a 250 ml. three-necked flask fitted with a mechanical stirrer, dropping funnel, and reflux condenser supporting a drying tube, 22.4 g. (0.1 mole) of ethyl-α-bromocaproate was added dropwise to a solution consisting of 100 ml. of ethylene glycol and 23 g. of anhydrous potassium fluoride. The temperature was maintained at 160-170° C. During the reaction, small amounts of ethanol were removed from the reaction mixture. After several additional hours of heating, the reaction solution was cooled, ether extracted, the ether dried and removed under vacuum. The remaining oil was fractionated to yield 6.0 g. of the corresponding unsaturated ester (b.p. 175-176° C.), and a considerable quantity of high-boiling residue. No α-fluorocaproate was obtained.

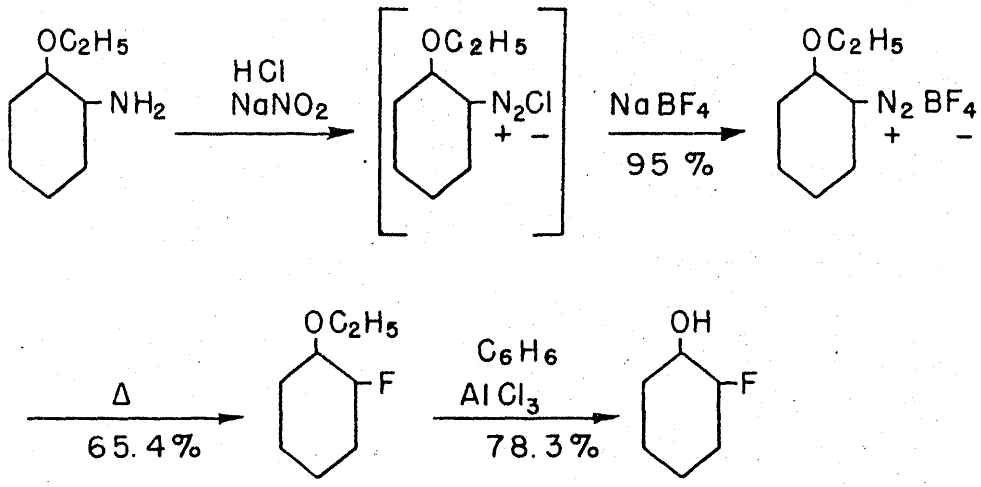
Method B:

Ethyl α-bromocaproate (22.4 g., 0.1 mole) and 28 g. (0.12 mole) of anhydrous mercuric fluoride were vigorously stirred and heated at 100° for four hours. The reaction mixture was cooled, ether added, and the mercuric bromide removed by filtration. The ethereal solution was dried, the ether removed under vacuum, and the resulting oil fractionated to yield the corresponding unsaturated ester (b.p. 175-176°). No α-fluorocaproate was obtained.

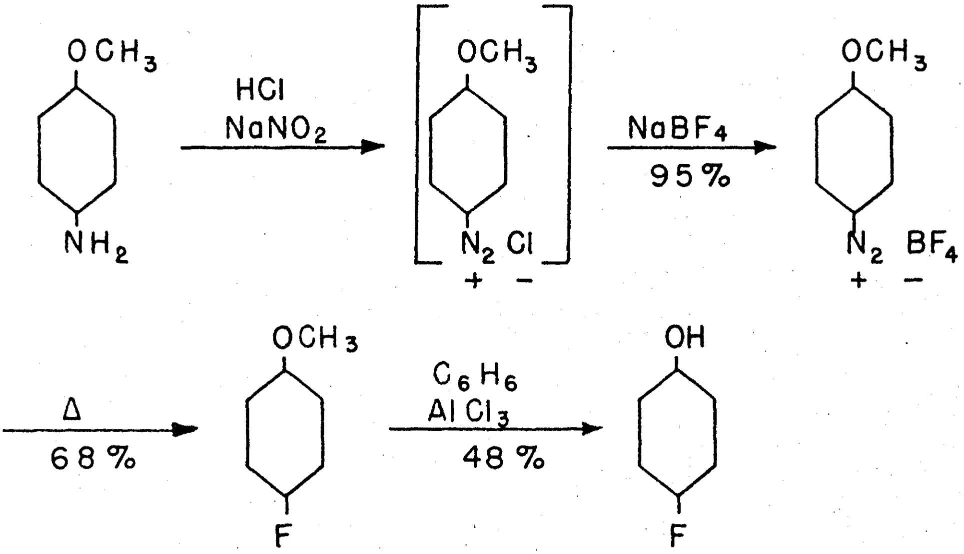
EXPERIMENTAL

III - Synthesis of Ortho, Meta and Para Fluorophenol

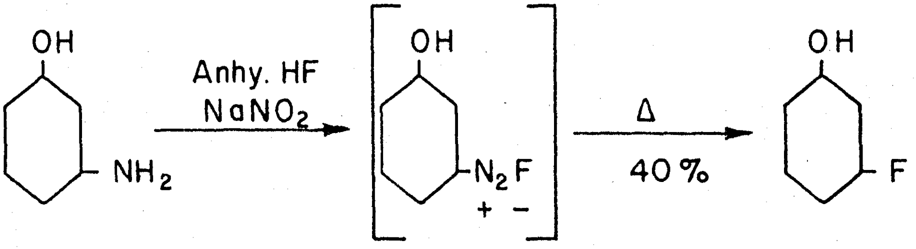
o-Fluorophenol:



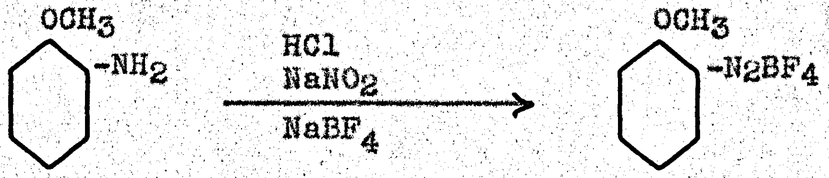
p-Fluorophenol:



m-Fluorophenol:



Preparation of o-Methoxydiazonium Fluoborate[55, 56]:



123 g. (1.0 mole)	222 g. (1.0 mole)
615 g. (5.0 moles)	1050 g. (4.73 moles)

$$\% \text{ Yield} = \frac{4.73}{5.0} = 95\%$$

o-Methoxydiazonium fluoborate was prepared by the Schiemann reaction as an intermediate in the synthesis of o-fluorophenol.

To a large metal beaker, equipped with a mechanical stirrer and thermometer and cooled in an ice bath, 615 g. (5.0 moles) of anisidine, 1400 ml. of water, and 1200 ml. of concentrated hydrochloric acid were added, with efficient stirring. During the course of 45 minutes, 385 g. (5.5 moles) of moist sodium nitrite, along with small lumps of dry ice to keep the temperature below 5° C., was added to the stirred mixture.

After the addition of the sodium nitrite was complete, the stirring was continued for one half hour. Then an aqueous solution of 1200 g.

of sodium fluoborate was added rapidly, while the temperature was maintained below 10° C. The tan precipitate which appeared was removed by filtration while the solution was still cold and washed, first with cold methanol and then with cold ether. The precipitate was air dried to yield 1050 g. (95%) of o-methoxydiazonium fluoborate.

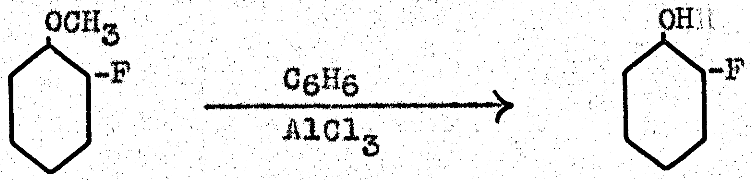
Preparation of o-Fluoroanisole:

222 g. (1.0 mole)	126 g. (1.0 mole)
1050 g. (4.73 moles)	390 g. (3.09 moles)

$$\% \text{ Yield} = \frac{3.09}{4.73} = 65.4\%$$

The dry o-methoxydiazonium fluoborate (1050 g., 4.73 moles) was divided into three equal portions and each portion decomposed by heating in a 2 l. round bottom flask fitted with a condenser and receiver. A water trap was connected to the receiving flask. The flask was heated carefully with a small flame, and the material decomposed smoothly. Toward the end of the decomposition, the flask was heated strongly to distill the last traces of product. The crude products were collected, combined, and steam distilled. The distillate was ether extracted, and the ether dried over anhydrous sodium sulfate. The ether was removed and the residue distilled at 158-159° C. under atmospheric conditions to yield 346 g. (65.4%) of o-fluoroanisole.

Preparation of o-Fluorophenol[57, 58, 59]:



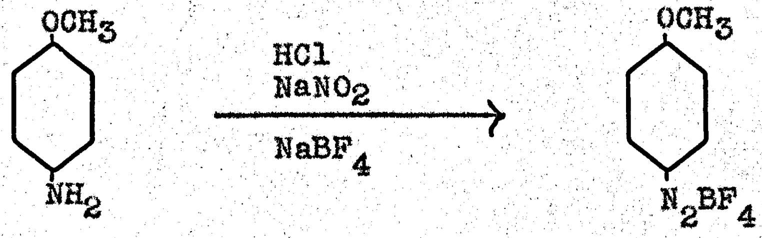
126 g. (1.0 mole)	112 g. (1.0 mole)
126 g. (1.0 mole)	88 g. (0.783 mole)

$$\% \text{ Yield} = \frac{0.783}{1.00} = 78.3\%$$

A mixture of 126 g. (1.0 mole) of o-fluoroanisole, 300 ml. of benzene, and 340 g. (2.48 moles) of aluminum chloride were refluxed for five hours in a 1 l. flask. The resulting mass was added slowly to an ice-water mixture. The water layer was separated and extracted with two 100 ml. portions of benzene.

The combined benzene extracts were thoroughly mixed with 400 ml. of 20% sodium hydroxide and the sodium hydroxide solution was then acidified and ether extracted. The ether solution was dried over anhydrous calcium sulfate, the ether removed, and the residue distilled at 147-149° C. to yield 88 g. (78.5 %) of *o*-fluorophenol.

Preparation of *p*-Methoxydiazonium Fluoborate[55, 56]:



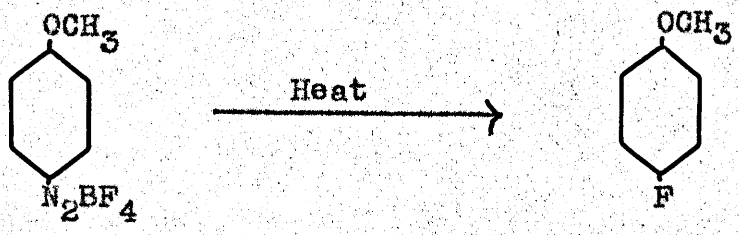
123 g. (1.0 mole)	222 g. (1.0 moles)
369 g. (3.0 moles)	634 g. (2.85 moles)

$$\% \text{ Yield} = \frac{2.85}{3.00} = 95\%$$

To a large metal beaker, equipped with a mechanical stirrer and thermometer and cooled in an ice bath, 369 g. (3.0 moles) of *p*-anisidine, 850 ml. of water, and 720 ml. of concentrated hydrochloric acid were added, with efficient stirring. During the course of 45 minutes, 228 g. (3.3 moles) of moist sodium nitrite, along with small lumps of dry ice to keep the temperature below 5° C., was added to the stirred mixture.

After the addition of the sodium nitrite was complete, the stirring was continued for one half hour. Then an aqueous solution of 720 g. of sodium fluoborate was added rapidly, while the temperature was maintained below 10°C. The tan precipitate which appeared was removed by filtration while the solution was still cold and washed, first with cold methanol and then with cold ether. The precipitate was air dried to yield 634 g. (95%) of p-methoxydiazonium fluoborate.

Preparation of p-Fluoroanisole:

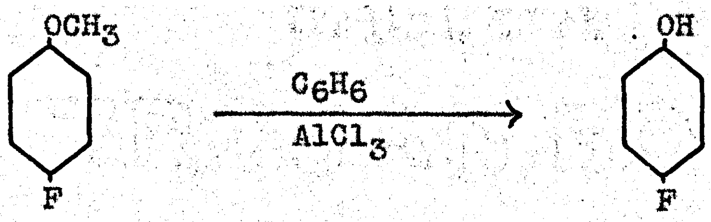


222 g. (1.0 mole)	126 g. (1.0 mole)
634 g. (2.85 moles)	244 g. (1.94 moles)

$$\% \text{ Yield} = \frac{1.94}{2.85} = 68\%$$

The dry p-methoxydiazonium fluoborate (634 g., 2.85 moles) was decomposed by heating in a 2 l. round bottom flask fitted with a condenser and receiver. A water trap was connected to the receiving flask. The flask was heated carefully with a small flame, and the material decomposed smoothly. Toward the end of the decomposition, the flask was heated strongly to distill the last traces of product. The crude products were collected, combined, and steam distilled. The distillate was ether extracted, the ether treated with ammonia gas, dried over calcium sulfate, and filtered. The ether was removed and the residue distilled at 156-157° C. under atmospheric conditions to yield 244 g. (68%) of p-fluoroanisole.

Preparation of p-Fluorophenol[57, 58, 59]:

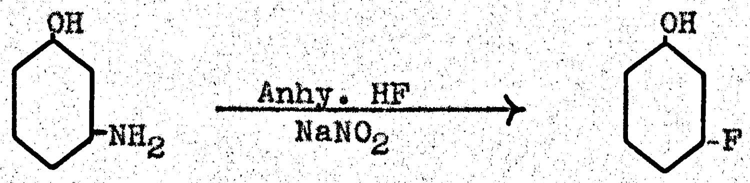


126 g. (1.0 mole)	112 g. (1.0 mole)
244 g. (1.94 moles)	104 g. (0.93 mole)

$$\% \text{ Yield} = \frac{0.93}{1.94} = 48\%$$

A mixture of 244 g. (1.94 moles) of *p*-fluoroanisole, 600 ml. of benzene, and 685 g. (5.0 moles) of aluminum chloride were refluxed for five hours in a 3 l. flask. The resulting mass was added slowly to an ice-water mixture. The water layer was separated and extracted with two 100 ml. portions of benzene. The combined benzene extracts were thoroughly mixed with 800 ml. of 20% sodium hydroxide and the sodium hydroxide solution was then acidified and ether extracted. The ether solution was dried over anhydrous calcium sulfate, the ether removed, and the residue distilled at 184-185° C. to yield 104 g. (48%) of *p*-fluorophenol.

Preparation of *m*-Fluorophenol[60]:



109 g. (1.0 mole)	112 g. (1.0 mole)
218 g. (2.0 moles)	90 g. (0.80 mole)

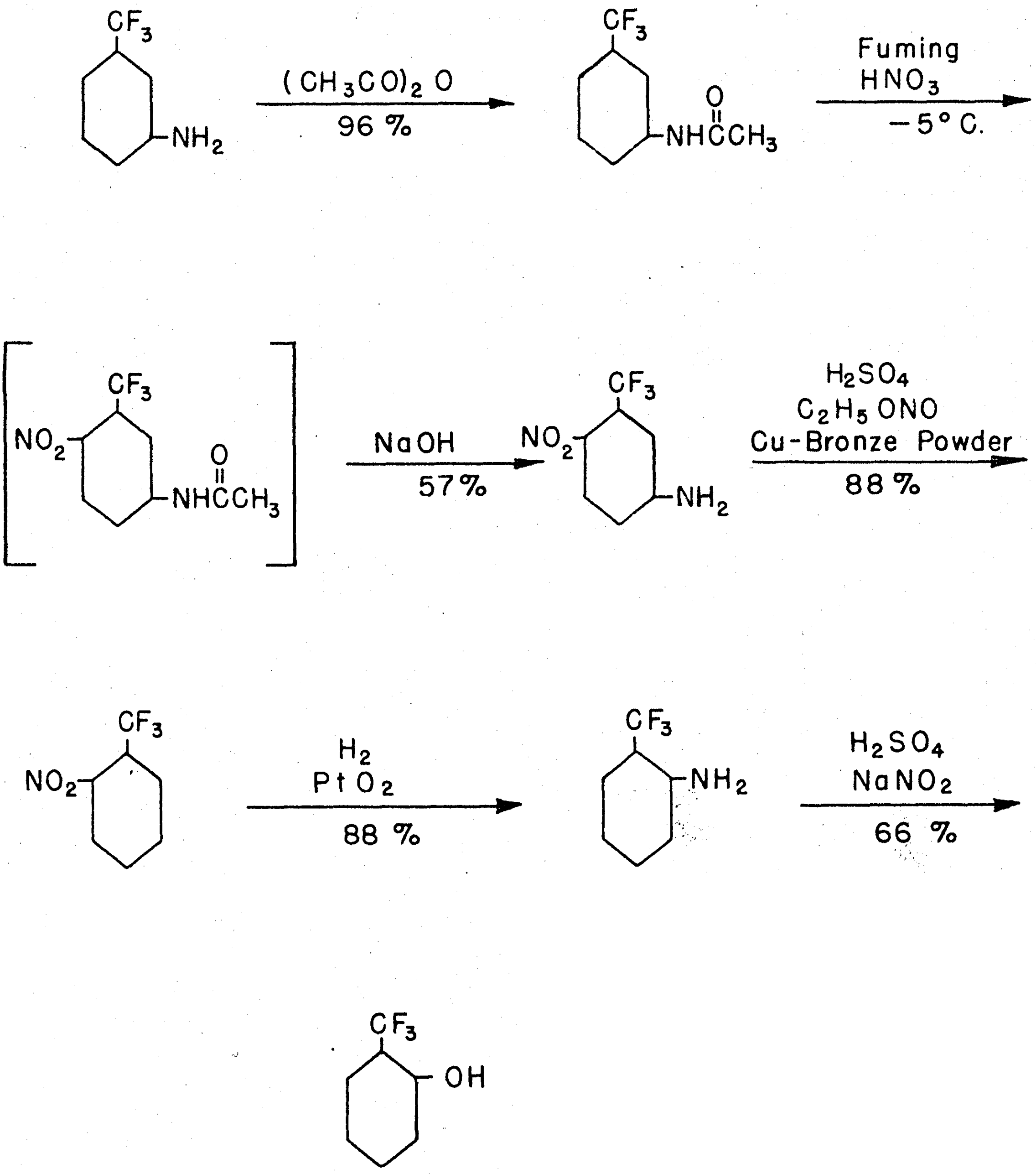
$$\% \text{ Yield} = \frac{0.80}{2.00} = 40\%$$

Approximately 800 g. (20 moles) of anhydrous hydrogen fluoride was added to 218 g. (2.0 moles) of m- aminophenol in a 3 l. stainless steel flask equipped with an efficient mechanical stirrer, and was maintained at a temperature of 5° C. by means of external cooling. During the course of an hour, 166 g. (2.4 moles) of solid sodium nitrite were added. The reaction mixture was then attached to an ice-cooled reflux coil, allowed to come to room temperature, and then slowly heated to 45° C. until nitrogen gas ceased to be liberated.

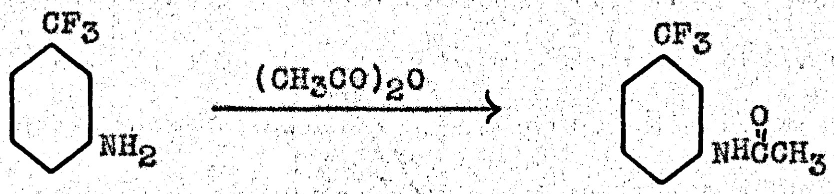
Dilution with ice water, followed by steam distillation, gave an insoluble oil which was dried over calcium sulfate and distilled to yield 90 g. (40%) of m-fluorophenol, boiling at 85-6° C. at 34 mm.

EXPERIMENTAL

IV - Synthesis of o- Trifluoromethylphenol :



Preparation of *m*-Trifluoromethylacetanilide[61]:

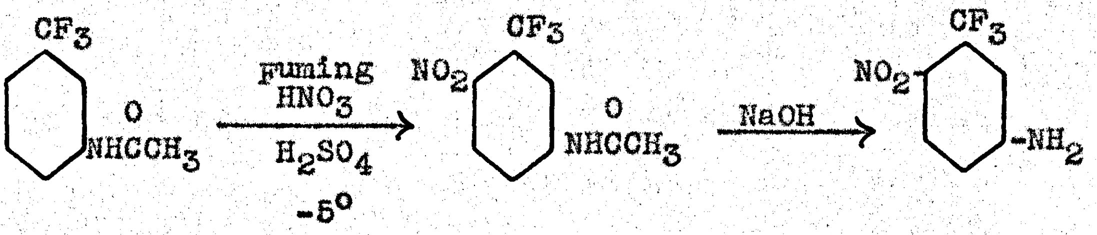


161 g. (1.0 mole)	204 g. (1.0 mole)
322 g. (2.0 moles)	387 g. (1.9 moles)

$$\% \text{ Yield} = \frac{1.9}{2.0} = 95\%$$

Two moles of *m*-aminobenzotrifluoride (322 g.) and approximately an equal weight of acetic anhydride were refluxed together for 24 hours. The acetic anhydride was in large measure removed by distillation, and the remaining solution poured into cold water. The resulting solids were filtered, washed, and dried, to yield 387 g. (95%) of crude *m*-trifluoromethylacetanilide. The crude material, melting at 101.2° - 102.0°, (Lit. 103°) was sufficiently pure for its desired use. Recrystallization from hot water gave white crystals, melting at 102.4° - 103.0° C.

Preparation of 2-Nitro-5-Aminobenzotrifluoride[62,63]:



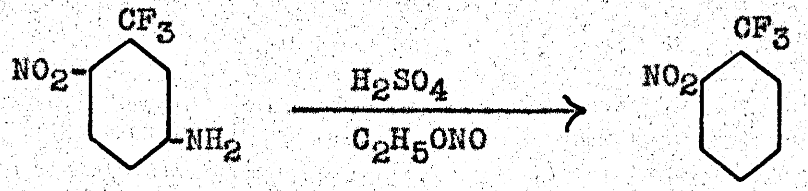
204 g. (1.0 mole)	206 g. (1.0 mole)
204 g. (1.0 mole)	117 g. (0.57 mole)

$$\% \text{ Yield} = \frac{0.57}{1.00} = 57\%$$

In a 2 l. flask equipped with a mechanical stirrer, dropping funnel, and thermometer, was placed one liter of concentrated sulfuric acid. This was cooled to -5° C., 204 g. (1.0 mole) of m-trifluoromethylacetanilide added, and the mixture stirred until a clear solution resulted. A solution of 81 g. of fuming nitric acid in 100 ml. of concentrated sulfuric acid was added dropwise during one hour, while the temperature was maintained at -5° by the addition of small lumps of dry ice. The solution was allowed to warm to room temperature and stand for three hours, then warmed to 40° for one hour, and poured upon crushed ice. The yellow, gummy precipitate which formed gradually crystallized and was then washed thoroughly with water.

The crude 3-trifluoromethyl-4-nitroacetanilide was immediately added to a solution of 200 ml. of 50% sodium hydroxide in 750 ml. of alcohol. The resulting dark solution was refluxed for 12 hours, evaporated to about two-thirds its original volume, and poured into a large quantity of cold water. The resulting solids were collected, washed with water, and air dried, and yielded 117 g. (57%) of 2-nitro-5-aminobenzotrifluoride, melting at 125-126° C.

Preparation of o-Nitrobenzotrifluoride:[62]

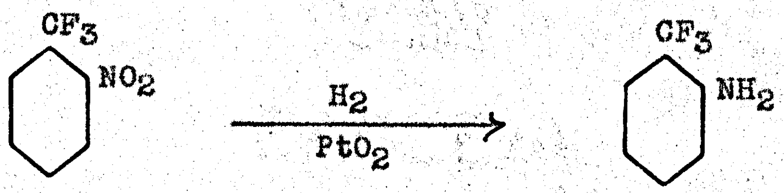


206 g. (1.0 mole)	191 g. (1.0 mole)
117 g. (0.57 mole)	95 g. (0.50 mole)

$$\% \text{ Yield} = \frac{0.50}{0.57} = 88\%$$

A solution consisting of 117 g. (0.57 mole) of crude 2-nitro-5-aminobenzotrifluoride in 500 ml. of absolute alcohol was cooled to 0° C., and, with stirring, 102 g. (1.04 moles) of concentrated sulfuric acid was slowly added. The solution was maintained at 0° C. while 79 g. (1.04 moles) of ethyl nitrite was added dropwise over a period of 45 minutes. After an additional hour, the solution was allowed to warm to 15°, and 1 g. of copper-bronze powder was added. Evolution of nitrogen began immediately, and the mildly exothermic reaction was allowed to proceed until the temperature reached 40°, where it was held until the evolution of nitrogen stopped. The solution was then boiled for 15 minutes, diluted with 1 liter of water, and extracted with five 150 ml. portions of chloroform. The chloroform was dried over magnesium sulfate, removed by distillation, and the resulting oil fractionated to yield 95 g. (88%) of o-nitrobenzotrifluoride, boiling at 106-108° C. at 20 mm.

Preparation of o-Aminobenzotrifluoride:

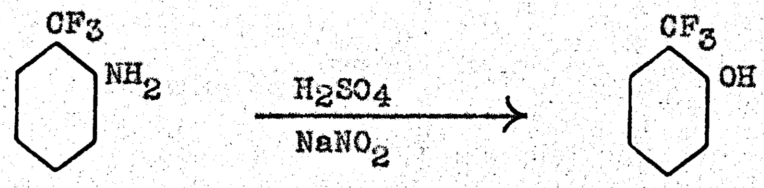


191 g. (1.0 mole)	161 g. (1.0 mole)
95 g. (0.50 mole)	71 g. (0.44 mole)

$$\% \text{ Yield} = \frac{0.44}{0.50} = 88\%$$

A mixture of 95 g. (0.50 mole) of *o*-nitrobenzotrifluoride and 0.2 g. of platinium oxide was shaken with hydrogen in a Parr hydrogenator at 50 p.s.i. until no more hydrogen was absorbed. The water and catalyst were separated and the *o*-aminobenzotrifluoride distilled at 66-68° C. (15 mm.) to give a yield of 71 g. (88%).

Preparation of *o*-Trifluoromethylphenol:



161 g. (1.0 mole)	162 g. (1.0 mole)
71 g. (0.44 mole)	47 g. (0.29 mole)

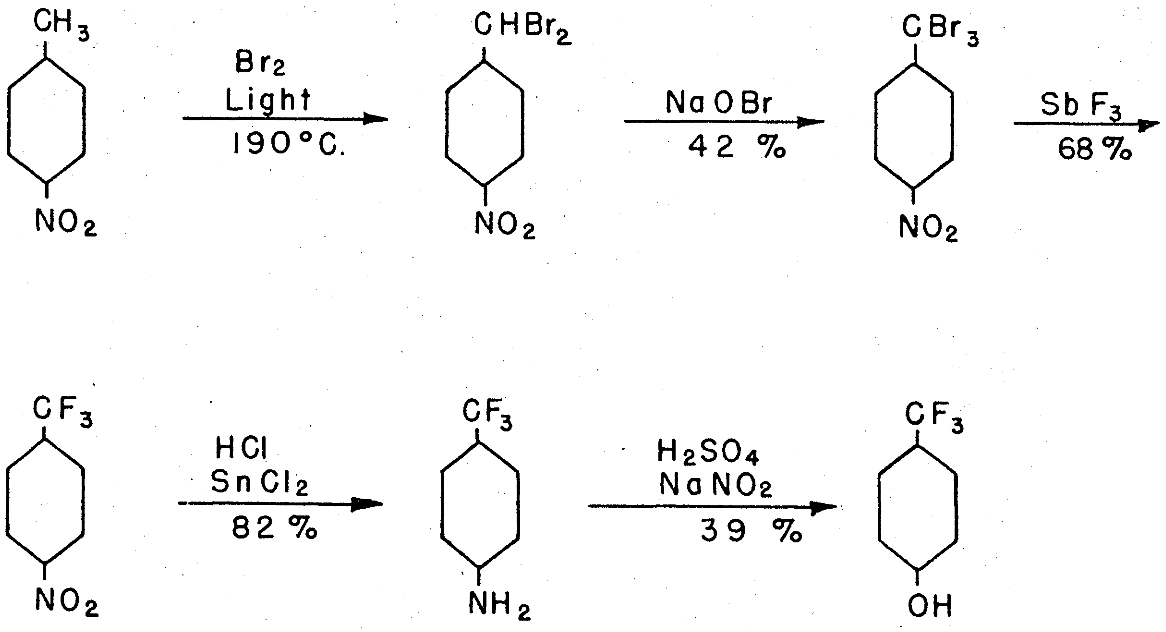
$$\% \text{ Yield} = \frac{0.29}{0.44} = 66\%$$

A solution consisting of 800 ml. of water, 220 g. of sulfuric acid, and 71 g. (0.44 moles) of *o*-aminobenzotrifluoride was cooled to 5°, and 35 g. (0.50 mole) of sodium nitrite was slowly added, with vigorous agitation. The mixture was stirred for an additional half hour and then slowly warmed to 50°, maintained there for one hour, and finally steam distilled. The resulting oil was extracted with ether, the ether solution dried over calcium sulfate, the ether removed by distillation, and the oil fractionated, to yield 47 g. (66%) of _o_-trifluoromethylphenol, boiling at 81-83° C. at 22mm.

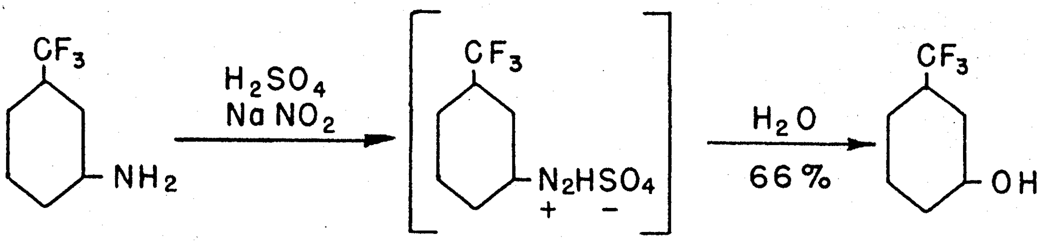
EXPERIMENTAL

V - Synthesis of Para- and Meta-Trifluoromethylphenol

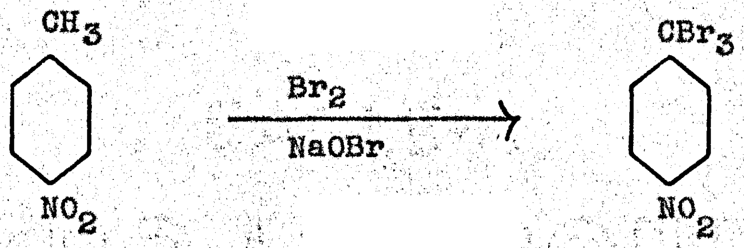
p-Trifluoromethylphenol:



m-Trifluoromethylphenol:



Preparation of p-Nitrobenzotribromide[62,64]:

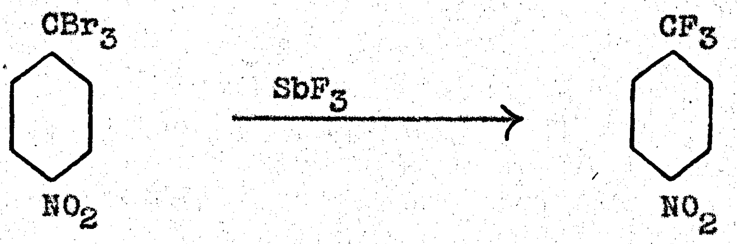


137 g. (1.0 mole)	374 g. (1.0 mole)
96 g. (0.70 mole)	110 g. (0.294 mole)

$$\% \text{ Yield} = \frac{0.294}{0.70} = 42\%$$

In a 500 cc. flask supporting a reflux condenser, dropping funnel and stirrer, 96 g. (0.7 mole) of p-nitrotoluene was heated to 195° and rapidly agitated while 280 g. (1.75 moles) of bromine was added dropwise over a period of two hours. The resulting solid material was leached with 1.5 l. of hot petroleum ether; considerable tar was left behind in this process. The petroleum ether solution was evaporated to 300 ml., and chilled to 0°. The solids were then separated and dissolved in 400 ml. of hot methanol, and the resulting solution poured, with stirring, into 2 l. of ice water. The solids were filtered, washed with cold water, and added to a cold sodium hypobromite solution consisting of 180 g. of bromine, 180 g. of sodium hydroxide, and 1500 ml. of water. The suspension was occasionally shaken and allowed to stand for two days at room temperature. The solids were separated, washed, and recrystallized from hot methanol to yield 110 g. (42%) of *p*-nitrobenzotribromide, melting at 82-83° (Lit. 86).

Preparation of *p*-Nitrobenzotrifluoride[62]:

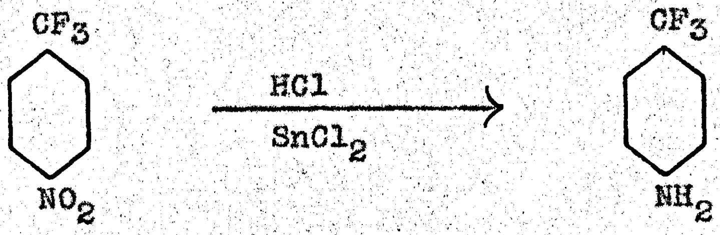


374 g. (1.0 mole)	191 g. (1.0 mole)
110 g. (0.294 mole)	38 g. (0.20 mole)

$$\% \text{ Yield} = \frac{0.200}{0.294} = 68\%$$

A mixture of 110 g. (0.294 mole) of *p*-nitrobenzotribromide and 58 g. (0.32 mole) of antimony fluoride was heated in a small round-bottom flask supporting a condenser set for distillation, until the mixture was entirely melted. Heating was continued and the mixture distilled, first at atmospheric pressure and finally under reduced pressure. Considerable solidification occurred in the condenser. The distillate was then dissolved in a mixture of 100 ml. of ether and a large excess of 12N hydrochloric acid. The ether was separated, washed with an excess of 10% sodium hydroxide, dried over calcium sulfate, and distilled, to yield 38 g. (68%) of p-nitrobenzotrifluoride, boiling at 84-85° (15 mm).

Preparation of p-Aminobenzotrifluoride:

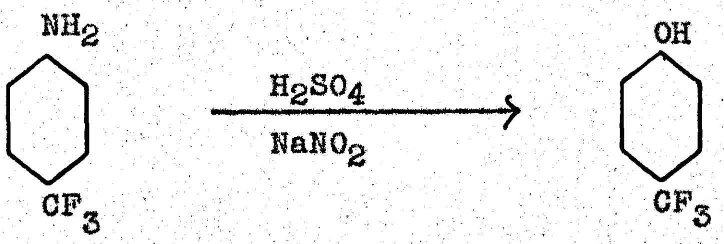


191 g. (1.0 mole)	161 g. (1.0 mole)
38 g. (0.20 mole)	26.4 g. (0.164 mole)

$$\% \text{ Yield} = \frac{0.164}{0.200} = 82\%$$

To a solution of 100 ml. of alcohol and 150 ml. of concentrated hydrochloric acid was added 38 g. (0.20 mole) of p-nitrobenzotrifluoride. The mixture was stirred and 200 g. of stannous chloride was added over the course of 30 minutes, while the temperature was maintained at 60°. The mixture was heated for an additional 30 minutes and then poured into a mixture of ice and 500 ml. of a 30% sodium hydroxide solution. The resulting mixture was extracted with ether, the ether solution dried over calcium sulfate, the solvent removed by distillation, and the resulting amine distilled to yield 26.4 g. (82%) of p-aminobenzotrifluoride, boiling at 89-90° C. (15 mm.).

Preparation of p-Trifluoromethylphenol:



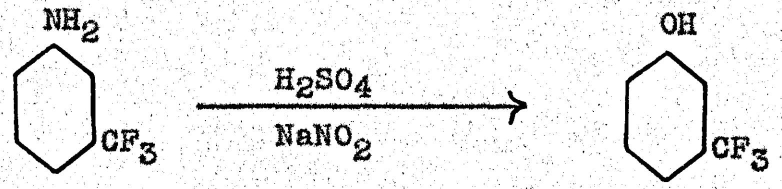
161 g. (1.0 mole)	162 g. (1.0 mole)
26.4 g. (0.164 mole)	10.4 g. (0.064 mole)

$$\% \text{ Yield} = \frac{0.064}{0.164} = 39\%$$

A 1 l. flask equipped with a mechanical stirrer was charged with 200 ml. of water, 25 ml. of sulfuric acid, and 26.4 g. (0.164 mole) of p-aminobenzotrifluoride, and the mixture cooled to 5°. Slowly, while the temperature was maintained at 5°, 11.7 g.

(0.17 mole) of sodium nitrite dissolved in 30 ml. of water was added. The resulting clear solution was gradually warmed, maintained at 50° for 30 minutes, and steam distilled. The resulting oil was extracted with ether, dried over calcium sulfate, and distilled at 80-81° (15 mm.), to yield 10.5 g. (39%) of p-trifluoromethylphenol.

Preparation of m-Trifluoromethylphenol[65]:



161 g. (1.0 mole)	162 g. (1.0 mole)
80.5 g. (0.5 mole)	53.5 g. (0.33 mole)

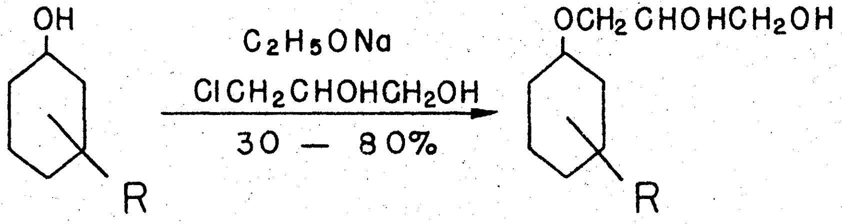
$$\% \text{ Yield} = \frac{0.33}{0.500} = 66\%$$

A 3 l. flask equipped with a mechanical stirrer was charged with 500 ml. of water, 65 ml. of sulfuric acid, and 80.5 g. (0.5 mole) of m-aminobenzotrifluoride. A heavy white suspension was obtained. This was cooled to 5° and 38.0 g. (0.55 mole) of sodium nitrite dissolved in 50 ml. of water was slowly added. The resulting clear solution was gradually warmed to room temperature, maintained at 50° for one hour, and then steam distilled. The resulting oil was extracted with ether, dried over calcium sulfate, and distilled at 84-85° C. (23 mm.), to yield 53.5 g. (66%) of *m*-trifluoromethylphenol.

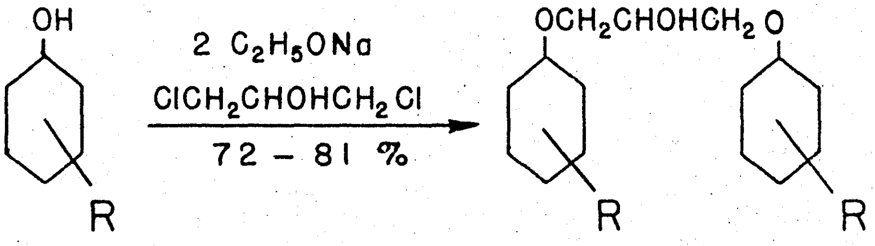
EXPERIMENTAL

VI- Synthesis of α and α-γ- Substituted Fluoro Ethers

α Substituted Glycerol Ethers:

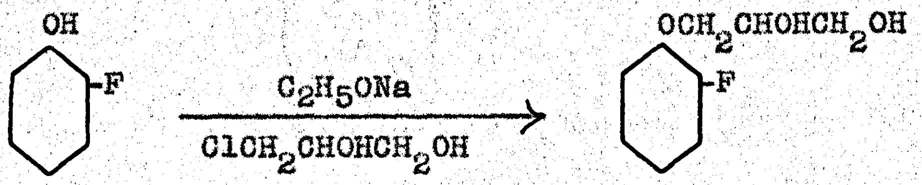


α-γ- Disubstituted Glycerol Ethers:



R = $-F$ (o,m,p); $-CF_3$ (o,m).

Preparation of 3-(2-fluorophenoxy)-propan-1,2-diol:[66]



112 g. (1.0 mole)	186 g. (1.0 mole)
11.2 g. (0.1 mole)	14.3 g. (0.077 mole)

$$\% \text{ Yield} = \frac{0.077}{0.100} = 77\%$$

To a sodium ethoxide solution, consisting of 250 ml. of absolute alcohol and 2.3 g. (0.1 mole) of sodium, 11.2 g. (0.1 mole) of o-fluorophenol was added. Glycerol-α-monochlorohydrin (12.1 g., 0.11 mole) was added to the resulting clear solution, and the mixture refluxed overnight. The salt was removed by filtration, the alcohol by distillation under atmospheric conditions, and the resulting oil dissolved in ether. The ethereal solution was washed with a dilute sodium hydroxide solution, then with dilute hydrochloric acid, and finally with water and dried over calcium sulfate. The ether was removed by distillation and the resulting oil fractionated to yield 14.3 g. (77%) of 3-(2-fluorophenoxy)-propan-1,2-diol, boiling at 154-156° (4 mm.). The high-boiling oil solidified upon cooling and was recrystallized from either a benzene-Skellysolve A mixture or from ether, the product melting at 42-43° C.

Anal. Calcd. for $C_9H_{11}O_3F$: C, 58.1; H, 6.0. Found: C, 58.3; H, 5.9.

Preparation of 3-(3-fluorophenoxy)-propan-1,2-diol:

This compound was prepared from m-fluorophenol by the general method described in the preceding section, using similar quantities and techniques. The yield of 3-(3-fluorophenoxy)-propan-1,2-diol, boiling at 162-163° (4 mm.), was 11.2 g. (61%): m.p. 47-48°.

Anal. Calcd. for $C_9H_{11}O_3F$: C, 58.1; H, 6.0. Found: C, 57.8; H, 5.9.

Preparation of 3-(4-fluorophenoxy)-propan-1,2-diol:

This compound was prepared from p-fluorophenol using the quantities and techniques indicated in the preceding sections. The yield of 3-(4-fluorophenoxy)-propan-1,2-diol, boiling at 163-164° (4 mm.) was 14.9 g. (80%): m.p. 53-54°.

Anal. Calcd. for $C_9H_{11}O_3F$: C, 58.1; H, 6.0. Found: C, 58.5; H, 6.2.

Preparation of 3-(2-trifluoromethylphenoxy)-propan-1,2-diol:

3-(2-trifluoromethylphenoxy)-propan-1,2-diol was prepared (as described in the preceding sections) from 17.8 g. (0.11 mole) of o-trifluoromethylphenol. Because the o-trifluoromethylphenol is not stable in basic solution, the sodium ethoxide solution was added to a slight excess of the phenol. Also, the oil finally obtained was not washed with dilute sodium hydroxide, but was fractionated directly. Otherwise the quantities and techniques are similar to those described in the preceding sections. The yield of 3-(2-trifluoromethylphenoxy)-propan-1,2-diol, boiling at 150-151° (4 mm.) was 7.2 g. (30%): m.p. 63-64°.

Anal. Calcd. for $C_{10}H_{11}O_3F_3$: C, 50.9; H, 4.7. Found: C, 50.8; H, 4.8.

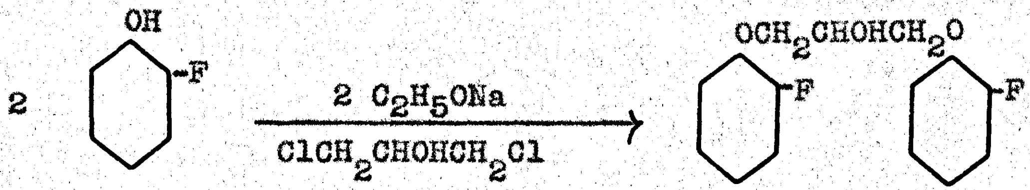
Preparation of 3-(3-trifluoromethylphenoxy)-propan-1,2-diol:

3-(3-trifluoromethylphenoxy)-propan-1,2-diol was prepared from 17.8 g. (0.11 mole) of m-trifluoromethylphenol, by the general method described in the preceding sections. m-Trifluoromethylphenol is sufficiently stable in basic solution to allow the oil obtained to be purified by washing with a dilute sodium hydroxide solution. The yield of 3-(3-trifluoromethylphenoxy)-propan-1,2-diol, boiling at 153-155° (4 mm.), was

15.6 g. (66%): m.p. 52-53°.

Anal. Calcd. for $C_{10}H_{11}O_3F_3$: C, 50.9; H, 4.7. Found: C, 51.1; H, 5.0.

Preparation of 1,3-di-(2-fluorophenoxy)-2-propanol:



112 g. (1.0 mole) 280 g. (1.0 mole)

11.2 g. (0.1 mole) 10.8 g. (0.04 mole)

$$\% \text{ Yield} = \frac{0.08}{0.10} = 80\%$$

To a solution of sodium ethoxide prepared by the addition of 2.3 g. (0.10 mole) of sodium to 250 ml. of absolute alcohol, there was added 11.2 g. (0.10 mole) of o-fluorophenol. Following the addition of 6.5 g. (0.05 mole) of glycerol-α-γ-dichlorohydrin to the resulting clear solution, the mixture was refluxed overnight. The salt was removed by filtration, the alcohol by distillation under atmospheric conditions, and the resulting oil was taken up in ether. The ethereal solution was washed with dilute sodium hydroxide, then with dilute hydrochloric acid, and finally with water. The ether was dried over calcium sulfate, removed by distillation, and the resulting oil fractionated to yield 10.8 g. (80%) of 1,3-di-(2-fluorophenoxy)-2-propanol, boiling at 180-182° (3 mm.). The high-boiling oil solidified upon cooling and was recrystallized from either a benzene-Skellysolve A mixture or from ether, to give a product melting at 53-54°.

Anal. Calcd. for $C_{18}H_{14}O_3F_2$: C, 64.3; H, 5.0. Found: C, 64.7; H, 5.4.

Preparation of 1,3-di-(3-fluorophenoxy)-2-propanol:

1,3-di-(3-fluorophenoxy)-2-propanol was prepared from m-fluorophenol by the method described in the preceding section. The yield was 12.1 g. (86%); b.p. 189-190° (4 mm.); m.p. 61-62°.

Anal. Calcd. for $C_{18}H_{14}O_3F_2$: C, 64.3; H, 5.0. Found: C, 64.5; H, 4.7.

Preparation of 1,3-di-(4-fluorophenoxy)-2-propanol:

1,3-di-(4-fluorophenoxy)-2-propanol was prepared from p-fluorophenol as described in the above sections. The yield was 10.1 g. (72%); b.p. 192-193° (3 mm.); m.p. 81-82° C.

Anal. Calcd. for $C_{18}H_{14}O_3F_2$: C, 64.3; H, 5.0. Found: C, 64.5; H, 5.0.

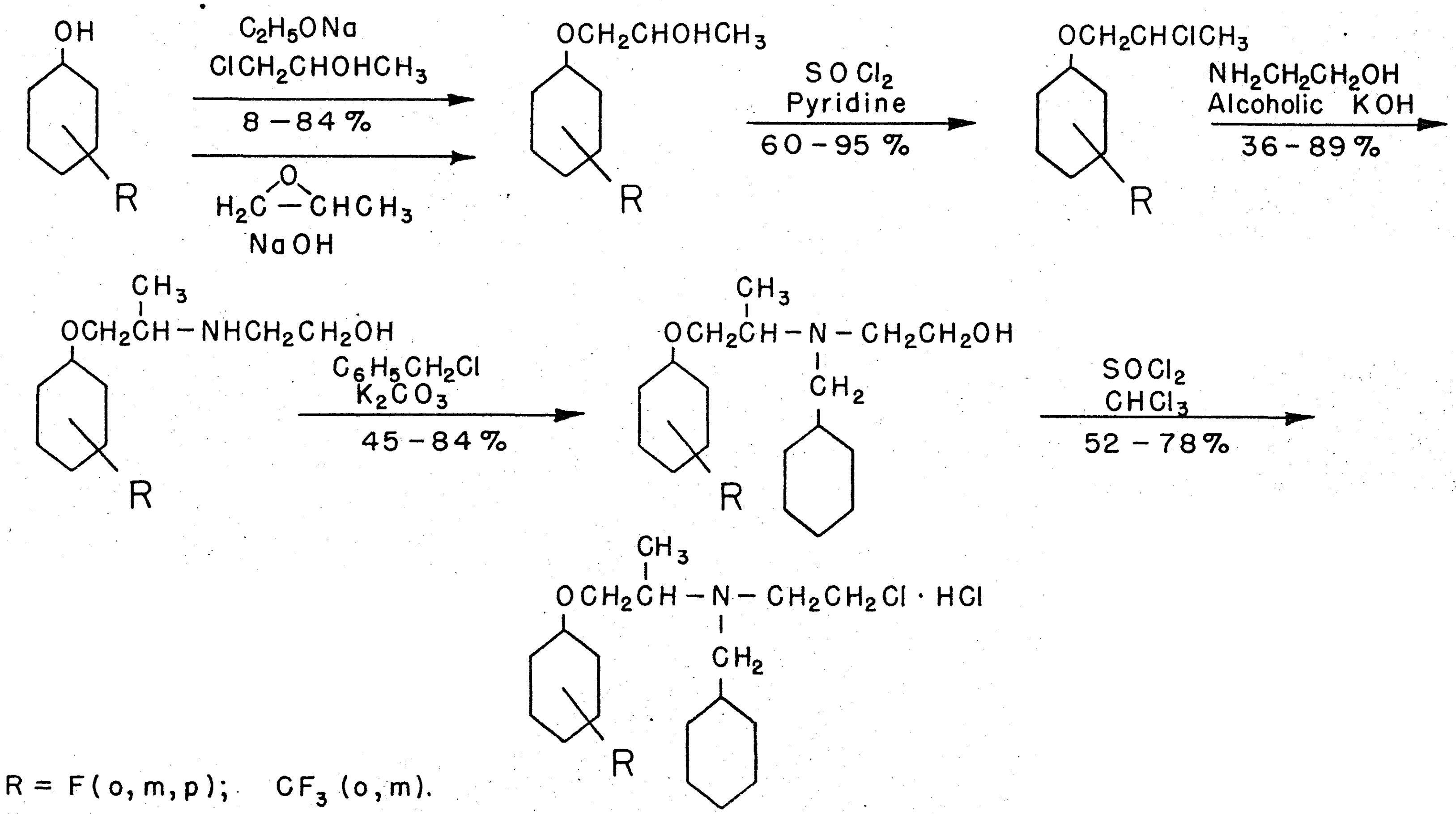
Preparation of 1,3-di-(3-trifluoromethylphenoxy)-2-propanol:

1,3-di-(3-trifluoromethylphenoxy)-2-propanol was prepared according to the exact procedure described for 1,3-di-(2-fluorophenoxy)-2-propanol, except that 17.8 g. (0.11 mole) of m-trifluoromethylphenol was substituted for the 11.2 g. of o-fluorophenol. The yield of pure product was 13.0 g. (68%); b.p. 165-166° (0.5 mm.); m.p. 58-59°.

Anal. Calcd. for $C_{17}H_{14}O_3F_6$: C, 53.7; H, 3.7. Found: C, 53.9; H, 3.9.

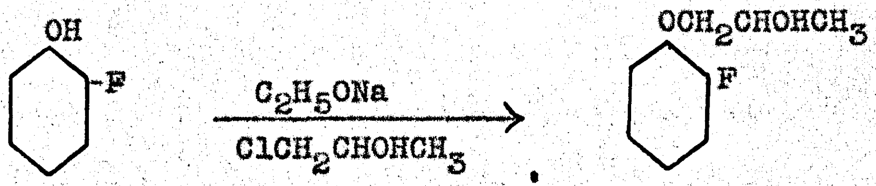
EXPERIMENTAL

VII - Synthesis of Fluoro- and Trifluoromethyl-Substituted *N*-(β-phenoxyisopropyl)-*N*-benzyl-β-chloroethylamines.



R = F(o, m, p); CF_3 (o, m).

Preparation of 1-(2-fluorophenoxy)-2-propanol[67]:



112 g. (1.0 mole)	170 g. (1.0 mole)
33.6 g. (0.3 mole)	40 g. (0.234 mole)

$$\% \text{ Yield} = \frac{0.234}{0.300} = 78.4\%$$

To a sodium ethoxide solution made by the addition of 6.9 g. (0.3 mole) of sodium to 250 ml. of absolute alcohol, 33.6 g. (0.3 mole) of o-fluorophenol was added. Propylene monochlorohydrin (29.4 g., 0.31 mole) was added to the resulting clear solution and the mixture refluxed overnight. The sodium chloride was removed by filtration, the alcohol by distillation, and the resulting oil was fractionated to yield 40 g. (78.4%) of 1-(2-fluorophenoxy)-2-propanol, boiling at 126-127° (17 mm.).

Anal. Calcd. for $C_9H_{11}O_2F$: C, 63.5; H, 6.5. Found: C, 63.7; H, 6.7.

Preparation of 1-(3-fluorophenoxy)-2-propanol:

1-(3-fluorophenoxy)-2-propanol was prepared from *m*-fluorophenol; quantities and conditions employed were similar to those described in the preceding section. The yield of 1-(3-fluorophenoxy)-2-propanol, a colorless oil, was 36.3 g. (71%), b.p. 124-125° (17 mm.).

Anal. Calcd. for $C_9H_{11}O_2F$: C, 63.5; H, 6.5. Found: C, 63.4; H, 6.4.

Preparation of 1-(4-fluorophenoxy)-2-propanol:

1-(4-fluorophenoxy)-2-propanol was prepared from *p*-fluorophenol in 84% yield under the conditions described in the preceding sections. It was obtained as a colorless oil boiling at 130-131° (17 mm.).

Anal. Calcd. for $C_9H_{11}O_2F$: C, 63.5; H, 6.5. Found: C, 63.7; H, 6.4.

Preparation of 1-(2-trifluoromethylphenoxy)-2-propanol:

1-(2-trifluoromethylphenoxy)-2-propanol was prepared by the reaction of 34.0 g. (0.21 mole) of *o*-trifluoromethylphenol, 4.6 g. (0.2 mole) of sodium, and 20 g. (0.21 mole) of propylene monochlorohydrin in absolute alcohol, by the method described in the preceding sections. The optimum yield of pure product, a colorless oil boiling at 116-117° (15 mm.), was 3.5 g. (8%).

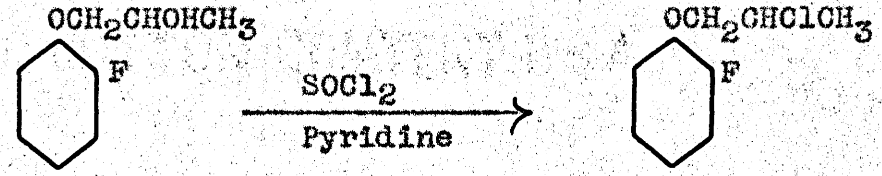
Anal. Calcd. for $C_{10}H_{11}O_2F_3$: C, 54.5; H, 5.0. Found: C, 54.4; H, 4.9.

Preparation of 1-(3-trifluoromethylphenoxy)-2-propanol:

1-(3-trifluoromethylphenoxy)-2-propanol was prepared from m-trifluoromethylphenol according to the directions given in the preceding section. The yield of pure product, a colorless oil boiling at 120-122° (15 mm.) was 30 g. (68%).

Anal. Calcd. for $C_{10}H_{11}O_2F_3$: C, 54.5; H, 5.0. Found: C, 54.4; H, 5.0.

Preparation of 1-(2-fluorophenoxy)-2-chloropropane[68]:



170 g. (1.0 mole)	189 g. (1.0 mole)
25.8 g. (0.15 mole)	27 g. (0.143 mole)

$$\% \text{ Yield} = \frac{0.143}{0.150} = 95\%$$

Thionyl chloride (23 g., 0.17 mole) was slowly added to 25.8 g. (0.15 mole) of 1-(2-fluorophenoxy)-2-propanol. After the original vigorous reaction, the mixture was shaken and allowed to stand until no additional hydrogen chloride fumes were liberated (approximately one hour). Several drops of pyridine were then added and the flask, fitted with a calcium chloride drying tube, was allowed to stand overnight. The mixture was then refluxed on a steam bath for two hours, excess thionyl chloride removed under vacuum, and the resulting oil dissolved in ether. The ethereal solution was washed with dilute hydrochloric acid, dried over calcium sulfate, the ether removed by distillation, and the oil fractionated to yield 27 g. (95%) of 1-(2-fluorophenoxy)-2-chloropropane, boiling at 109-110° (16 mm.).

Anal. Calcd. for $C_9H_{10}OFCl$: C, 57.3; H, 5.3. Found: C, 57.5; H, 5.4.

Preparation of 1-(3-fluorophenoxy)-2-chloropropane:

This compound was prepared from 1-(3-fluorophenoxy)-2-propanol by the general method described in the preceding section, similar quantities and techniques being employed. The yield of 1-(3-fluorophenoxy)-2-chloropropane, boiling at 109-110° (15 mm.) was 17 g. (60%).

Anal. Calcd. for $C_9H_{10}OFCl$: C, 57.3; H, 5.3. Found: C, 56.9; H, 5.6.

Preparation of 1-(4-fluorophenoxy)-2-chloropropane:

Preparation of this compound from 1-(4-fluorophenoxy)-2-propanol was accomplished by the general method described in the preceding sections. The yield of 1-(4-fluorophenoxy)-2-chloropropane, boiling at 110-111° (15 mm.) was 25.8 g. (90%).

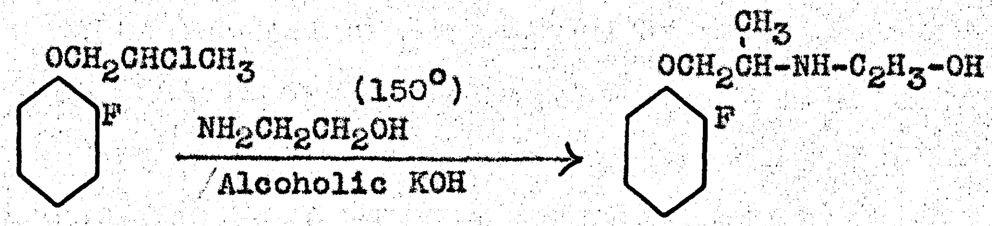
Anal. Calcd. for $C_9H_{10}OFCl$: C, 57.3; H, 5.3. Found: C, 57.7; H, 5.5.

Preparation of 1-(3-trifluoromethylphenoxy)-2-chloropropane:

This compound was prepared from 20 g. (0.091 mole) of 1-(3-trifluoromethylphenoxy)-2-propanol and 16 g. (0.12 mole) of thionyl chloride by the general method described in the preceding sections. The yield of 1-(3-trifluoromethylphenoxy)-2-chloropropane, boiling at 110-111° (15 mm.) was 14 g. (65%).

Anal. Calcd. for $C_{10}H_{10}OF\,Cl$: C, 50.3; H, 4.2. Found: C, 50.2; H, 4.3.

Preparation of N-[β-(2-fluorophenoxy) isopropyl]-ethanolamine[30,69,70]:



189 g. (1.0 mole)	213 g. (1.0 mole)
37.8 g. (0.2 mole)	32.4 g. (0.152 mole)

$$\% \text{ Yield} = \frac{0.152}{0.200} = 76\%$$

A mixture of 37.8 g. (0.2 mole) of 1-(2-fluorophenoxy)-2-chloropropane and 61 g. (1.0 mole) of redistilled ethanolamine was heated overnight at 150°, with vigorous agitation. The mixture was cooled, 12 g. (0.21 mole) of potassium hydroxide dissolved in absolute ethyl alcbhol added, and the resulting salt removed by filtration. The alcoholic solution was dried over calcium sulfate, the alcohol removed by distillation, and the resulting oil fractionated to yield 32.4 g. (76%) of N-[β-(2-fluorophenoxy) isopropyl]-ethanolamine, boiling at 148-149° (4 mm.). The high-boiling oil solidified upon cooling and was recrystallized from acetone to give a white crystalline material melting at 54.2-55.0°.

Anal. Calcd. for $C_{11}H_{16}O_2NF$: N, 6.6; Found: N, 6.8.

Preparation of N-[β-(3-fluorophenoxy)isopropyl]-ethanolamine:

This compound was prepared from 1-(3-fluorophenoxy)-2-chloropropane by the general method described in the preceding section. The yield of N-[β-(3-fluorophenoxy) isopropyl]ethanolamine, boiling at 150-151° (4 mm.), m.p. 60.7-61.3°, was 38 g. (89%).

Anal. Calcd. for $C_{11}H_{16}O_2NF$: N, 6.6. Found: N, 6.6.

Preparation of N-[β-(4-fluorophenoxy) isopropyl]-ethanolamine:

This compound was prepared from 1-(4-fluorophenoxy)-2-chloropropane by the general method described in the preceding sections. The yield of N-[β-(4-fluorophenoxy) isopropyl]-ethanolamine, boiling at 152-153° (4 mm.), m.p. 71.8-72.4°, was 29 g. (68%).

Anal. Calcd. for $C_{11}H_{16}O_2NF$: N, 6.6. Found: N, 6.5.

Preparation of N-[β-(2-trifluoromethylphenoxy) isopropyl]-ethanolamine:

This compound was prepared from 7 g. (0.029 mole) of 1-(2-trifluoromethylphenoxy)-2-chloropropane and 3.7 g. (0.06 mole) of ethanolamine by the general method described in the preceding sections. The yield of N-[β-(2-trifluoromethylphenoxy) isopropyl]-ethanolamine, boiling at 145-147° (4 mm.), M.p. 64.2-65.0°, was 2.8 g. (36%).

Anal. Calcd. for $C_{12}H_{16}O_2NF$: N, 5.3. Found: N, 5.4.

Preparation of N-[β-(3-trifluoromethylphenoxy) isopropyl]-ethanolamine:

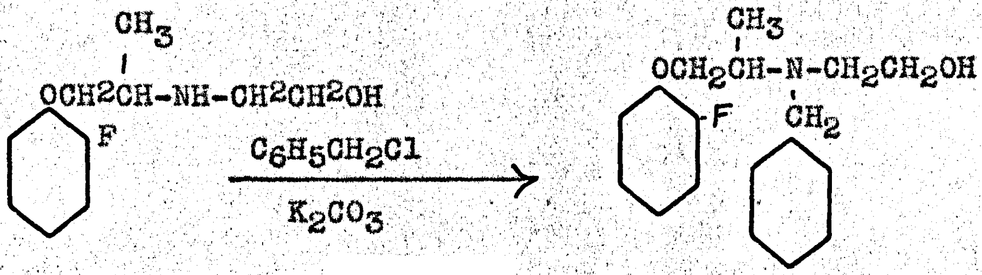
This compound was prepared from 42 g. (0.176 mole) of 1-(3-trifluoromethylphenoxy)-2-chloropropane and 61 g. (1.0 mole) of ethanolamine by the general method described in the preceding sections. The yield of N-[β-(2-trifluoromethylphenoxy) isopropyl]-ethanolamine, boiling at 149-150° (4 mm.), m.p. 88.8-89.2°, was 34 g. (73%).

<u>Anal.</u> Calcd. for $C_{12}H_{16}O_2NF_3$: N, 5.3. Found: N, 5.3.

Preparation of N-(β-phenoxyisopropyl)-ethanolamine:

This compound was prepared from 51 g. (0.3 mole) of 1-phenoxy-2-chloropropane and 92 g. (1.5 moles) of ethanolamine by the general method described in the preceding sections. The yield of N-[β-phenoxyisopropyl)-ethanolamine, boiling at 152-154° (4 mm.), m.p. 64.8-65.3°, was 44 g. (73%).

Preparation of N-[β-(2-fluorophenoxy) isopropyl]-N-benzylethanolamine[30,69,70]:



213 g. (1.0 mole)	303 g. (1.0 mole)
17 g. (0.08 mole)	20.4 g. (0.067 mole)

$$\% \text{ Yield} = \frac{0.067}{0.080} = 84\%$$

A solution consisting of 100 ml. of absolute alcohol, 17 g. (0.08 mole) of N-[β-(2-fluorophenoxy) isopropyl]-ethanolamine, 10.1 g. (0.08 mole) of benzyl chloride, and 6.9 g. (0.05 mole) of potassium carbonate was vigorously agitated and refluxed for twenty-four hours. The solids were removed by filtration, the alcohol distilled, and the resulting crude oil dissolved in 200 ml. of 10% hydrochloric acid. The acid solution was cooled to 5° and 6.9 g. (0.1 mole) of solid sodium nitrite slowly added, with vigorous stirring. After ½ hour, the cold solution was extracted with two 100 ml. portions of ether, made basic with 30% sodium hydroxide, and the basic solution extracted with three 100 ml. portions of ether. The latter ethereal solution was dried over calcium sulfate, the ether distilled, and the resulting oil fractionated to yield 20.4 g. (84%) of N-[β-(2-fluorophenoxy) isopropyl]-N-benzylethanolamine, boiling at 178-179° (0.5 mm.).

Anal. Calcd. for $C_{18}H_{22}O_2NF$: C, 71.3; H, 7.2; N, 4.6. Found: C, 71.3; H, 7.1; N, 4.8.

Preparation of N-[β-(3-fluorophenoxy) isopropyl]-N-benzylethanolamine:

This compound was prepared by the reaction of 21.3 g. (0.1 mole) of N-[β-(3-fluorophenoxy) isopropyl]-ethanolamine, 12.6 g. (0.1 mole) of benzyl chloride, and 8.3 g. (0.06 mole) of potassium carbonate in 100 ml. of absolute alcohol by the method described in the preceding section. The yield of N-[β-(3-fluorophenoxy) isopropyl]-N-benzylethanolamine, boiling at 174-175° (0.4 mm.) was 24 g. (79%).

Anal. Calcd. for $C_{18}H_{22}O_2NF$: C, 71.3; H, 7.2; N, 4.6. Found: C, 71.4; H, 7.5; N, 4.9.

Preparation of N-[β-(4-fluorophenoxy) isopropyl] -N-benzylethanolamine:

This compound was prepared by the condensation of N-[β-(4-fluorophenoxy) isopropyl]-ethanolamine and benzyl chloride by the general method described in the preceding sections. Similar quantities, conditions, and means of purification were used. The yield of N-[β-(4-fluorophenoxy) isopropyl] -N-benzylethanolamine, boiling at 180-181° (0.4 mm.) was 19 g. (79%).

Anal. Calcd. for $C_{18}H_{22}O_2NF$: C, 71.3; H, 7.2; N, 4.6. Found: C, 71.7; H, 7.0; N, 4.7.

Preparation of N-[β-(2-trifluoromethylphenoxy)-isopropyl] -N-benzylethanolamine:

This compound was prepared by the condensation of 2.8 g. (0.0106 mole) of N-[β-(2-trifluoromethylphenoxy) isopropyl] -ethanolamine and 1.3 g. (0.0106 mole) of benzyl chloride by the general method described in the preceding sections. The yield of N-[β-(2-trifluoromethylphenoxy) isopropyl] -N-benzylethanolamine, boiling at 168-169° (0.4 mm.), was 1.6 g. (45%).

Anal. Calcd. for $C_{19}H_{22}O_2NF_3$: C, 64.6; H, 6.3; N, 4.0.

Preparation of N-/β-(3-trifluoromethylphenoxy) isopropyl/ -N-benzylethanolamine:

This compound was prepared by the condensation of 26.3 g. (0.1 mole) of N-/β-(3-trifluoromethylphenoxy) isopropyl/ -ethanolamine and 12.6 g. (0.1 mole) of benzyl chloride as described in the preceding sections. The yield of N-/β-(3-trifluoromethylphenoxy) isopropyl/ -N-benzylethanolamine, boiling at 173-174° (0.5 mm.) was 29 g. (82%).

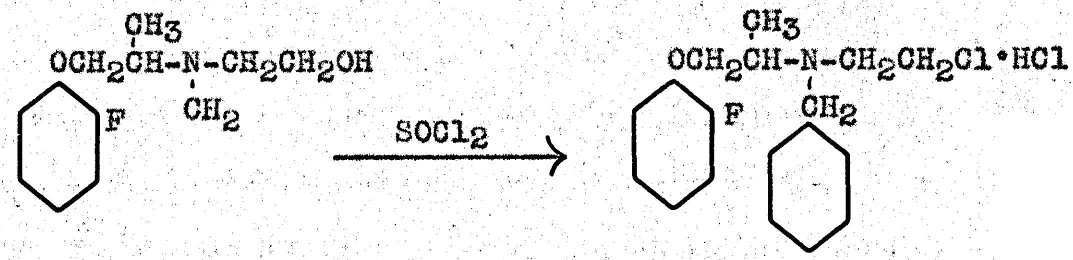
Anal. Calcd. for $C_{19}H_{22}O_2NF_3$: C, 64.6; H, 6.3; N, 4.0. Found: C, 64.7; H, 6.0; N, 4.2.

Preparation of N-(β -phenoxyisopropyl) -N-benzylethanolamine:

This compound was prepared by the condensation of 40 g. (0.2 mole) of N-(β -phenoxyisopropyl)-ethanolamine and 25.2 g. (0.2 mole) of benzyl chloride by the general method described in the preceding sections, utilizing similar conditions and means of purification. The yield of N-(β -phenoxyisopropyl) -N- benzylethanolamine, boiling at 182-183° (0.6 mm.), was 52 g. (91%).

Anal. Calcd for $C_{18}H_{23}O_2N$: C, 75.75; H, 8.12; N, 4.91. Found: C, 75.63; H, 7.91; N, 5.20.

Preparation of N-[β-(2-fluorophenoxy) isopropyl] -N-benzyl-β-chloroethylamine hydrochloride[30,69]



303 g. (1.0 mole)	358 g. (1.0 mole)
9.2 g. (0.0304 mole)	7.5 g. (0.0209 mole)

$$\% \text{ Yield} = \frac{0.0209}{0.0304} = 69\%$$

N-[β-(2-fluorophenoxy) isopropyl] -N-benzylethanolamine (9.2 g., 0.0304 mole) was gradually added to 25 ml. of redistilled thionyl chloride. After the initial vigorous reaction had subsided, the mixture was refluxed for one hour and the excess thionyl chloride removed under reduced pressure. The residue was recrystallized from an absolute alcohol-ether mixture and yielded 7.5 g. (69%) of N-[β-(2-fluorophenoxy) isopropyl] -N-benzyl-β-chloroethylamine hydrochloride melting at 158-159°.

Anal. Calcd. for $C_{18}H_{22}ONFCl_2$: C, 60.3; H, 6.2; N, 3.9.

Preparation of N-[β-(3-fluorophenoxy) isopropyl]-N-benzyl-β-chloroethylamine hydrochloride:

This compound was prepared by the action of thionyl chloride on 11.0 g. (0.0362 mole) of N-[β-(3-fluorophenoxy) isopropyl]-N-benzyl-ethanolamine as described in the preceding section. The yield of N-[β-(3-fluorophenoxy) isopropyl]-N-benzyl-β-chloroethylamine hydrochloride, melting at 140-141°, was 8.0 g. (62%).

Anal. Calcd. for $C_{18}H_{22}ONFCl_2$: C, 60.3; H, 6.2; N, 3.9.

Preparation of N-[β-(4-fluorophenoxy) isopropyl]-N-benzyl-β-chloroethylamine hydrochloride:

This compound was prepared by the action of thionyl chloride on 13.5 g. (0.0446 mole) of N-[β-(4-fluorophenoxy) isopropyl]-N-benzylethanolamine as described in the preceding sections. The yield of N-[β-(4-fluorophenoxy) isopropyl]-N-benzyl-β-chloroethylamine hydrochloride, melting at 136-137°, was 10.0 g. (69%).

Anal. Calcd. for $C_{18}H_{22}ONFCl_2$: C, 60.3; H, 6.2; N, 3.9.

Preparation of N-[β-(2-trifluoromethylphenoxy) isopropyl] -N-benzyl-β-chloroethylamine hydrochloride:

This compound was prepared by the action of thionyl chloride on 1.6 g. (0.0045 mole) of N-[β-(2-trifluoromethylphenoxy) isopropyl] -N-benzylethanolamine as described in the preceding sections. The yield of N-[β-(2-trifluoromethylphenoxy) isopropyl] -N-benzyl-β-chloroethylamine hydrochloride, melting at 141-142° was 0.95 g. (52%).

Anal. Calcd. for $C_{19}H_{22}ONF_3Cl_2$: C, 55.9; H, 5.4; N, 3.4.

Preparation of N-[β-(3-trifluoromethylphenoxy) isopropyl] -N-benzyl-β-chloroethylamine hydrochloride:

This compound was prepared by the action of thionyl chloride on 21.0 g. (0.0595 mole) of N-[β-(3-trifluoromethylphenoxy) isopropyl] -N-benzylethanolamine as described in the preceding sections. The yield of N-[β-(3-trifluoromethylphenoxy) isopropyl] -N-benzyl-β-chloroethylamine hydrochloride, melting at 146-147°, was 18 g. (74%).

Anal. Calcd. for $C_{19}H_{22}ONF_3Cl_2$: C, 55.9; H, 5.4; N, 3.4.

Preparation of N-(β-phenoxyisopropyl)-N-benzyl-β-chloroethylamine hydrochloride:

This compound was prepared by the action of thionyl chloride on 19 g. (0.0666 mole) of N-(β-phenoxyisopropyl)-N-benzylethanolamine as described in the previous sections. The yield of N-(β-phenoxyisopropyl)-N-benzyl-β-chloroethylamine hydrochloride, melting at - ° C., was 12 g. (53%).

Anal. Calcd. for $C_{18}H_{23}ONCl_2$: C, 63.72; H, 6.80; N, 4.13.

IV. DISCUSSION OF EXPERIMENTAL RESULTS

Fluoro Isosteres of Vitamin B_6:

The dibromo derivative of pyridoxine (Vitamin B_6) was obtained by treatment of pyridoxine with 40% hydrobromic acid. Attempted preparation of the difluoro analog by treatment of the dibromide with such halogen exchange agents as mercuric oxide and anhydrous hydrogen fluoride, mercuric fluoride and anhydrous hydrogen fluoride, mercuric fluoride and chloroform, and potassium fluoride and cellosolve, at a variety of temperatures up to 135°, yielded only resinous materials.

Fluoro Isosteres of Pantothenic Acid:

In the preparation of fluoro isosteres of pantothenic acid, the α-hydroxy-β,β-dimethyl-γ-butyrolactone portion of the molecule has been unsuccessfully treated with numerous halogenating agents in an effort to obtain the α-bromo or α-chloro lactone. Brominating agents such as red phosphorus and bromine, phosphorus tribromide, and phosphorus tribromide and bromine have failed to yield the completely brominated product. Attempted purification by molecular distillation and by crystallization failed to yield pure product.

Treatment of the lactone with thionyl chloride and a mixture of thionyl chloride and phosphorus pentachloride failed to yield the pure α-chloro lactone.

Fluoro Isosteres of Essential Amino Acids:

The preparation of fluorine-containing compounds in which fluorine replaces the isosteric amino group of the essential amino acids has been attempted through the δ-bromo acid ester analogs of such essential amino acids as leucine, isoleucine, norleucine, serine, and tyrosine. The bromine-fluorine halogen exchange reaction[54,70] was attempted, using mercuric fluoride and potassium fluoride[71,72,7] under various conditions. The halogen exchange was attempted in such solvents as chloroform, cellosolve, ethylene glycol, or in quinoline, as well as in the absence of any solvent, with variations in temperature between 45° and 190°. With mercuric fluoride, the halogen exchange was found to take place at 70-80° without the use of a solvent, but only the unsaturated ester and high-boiling products, presumably polymeric in nature, were obtained. With potassium fluoride and ethylene glycol, at temperatures above 140°, considerable amounts of ethanol were removed from the reaction mixture, probably the result of an alcohol interchange, with the glycol catalyzed by hydrofluoric acid liberated in the reaction. In none of the runs was any δ-fluoro ester or acid isolated.

The various bromo and fluoro derivatives of tyrosine which were prepared and the trichloroacetyl blocked substituted phenyl alanines were tested as anti-tularemia agents. Preliminary tests have indicated that α-bromo-β-(p-fluorophenyl) propionic acid and β-(p-fluorophenyl)-N-trichloroacetyl-alanine possess activity as anti-tularemia agents.

The various N-trichloroacetyl substituted phenyl alanines prepared failed to yield pure compounds. Several recrystallizations from acid solutions repeatedly gave a material slightly high in carbon and nitrogen content. A slight degree of hydrolysis of the chlorines or of the trichloroacetyl group is suspected.

Fluoro- and Trifluoromethylphenol:

The ortho- and para-fluorophenols were prepared in overall yields of 48 and 34% by the Schiemann reaction[55,56] on the corresponding anisidines, followed by cleavage of the ethers with aluminum chloride. A study of the Schiemann reaction on o-anisidine and o-phenetidine was made to determine which would give the best yield of the corresponding diazonium fluoborate. Little difference was noted in the two compounds as both gave yields of over 90%. m-Fluorophenol was readily prepared in 40% yields by direct diazotization of m-aminophenol in anhydrous hydrogen fluoride[60]. The trifluoromethylphenols were prepared according to the method of Jones[62].

Fluoro-Containing α- and α,γ-Substituted Glycerol Ethers:

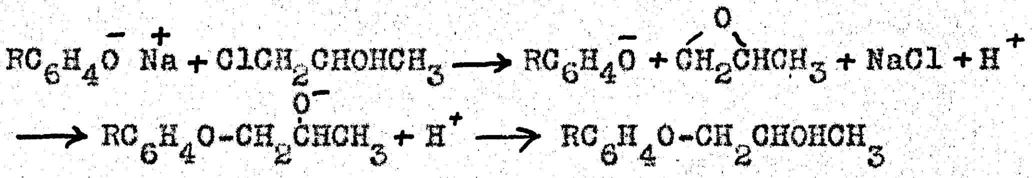
Fluoro-containing 3-phenoxypropan-1,2-diols were readily prepared in good yields by the condensation of the appropriate sodium fluorophenolate and glycerol-α-monochlorohydrin. The ortho and meta trifluoromethyl derivatives were prepared in a similar manner but the para trifluoromethylphenol was so unstable in basic solution that it was impossible to prepare the corresponding para derivative.

The α-γ-disubstituted glycerol ethers were successfully prepared by the condensation of two parts of the sodium phenolate with one part of glycerol-α,γ-dichlorohydrin.

The high boiling oil obtained in these runs solidified upon cooling and repeated recrystallization from a benzene-Skellysolve "B" mixture or from ether produced a white waxy solid.

Fluoro-Containing β-Chloroethylamines:

The preparation of fluoro-containing β-chloroethylamines of possible sympatholytic importance was achieved by the condensation of the appropriate fluoro or trifluoromethyl phenolate and propylene monochlorohydrin. The mechanism of this reaction was found to be the elimination of hydrogen chloride from the propylene monochlorohydrin to yield propylene oxide, followed by the attack of the phenolate ion on the propylene oxide to yield the secondary alcohol. This mechanism was



$$RC_6H_4\overset{-}{O}\ \overset{+}{Na} + ClCH_2CHOHCH_3 \longrightarrow RC_6H_4\overset{-}{O} + \overset{\diagup O \diagdown}{CH_2CHCH_3} + NaCl + H^+$$

$$\longrightarrow RC_6H_4O\text{-}CH_2\overset{O^-}{C}HCH_3 + H^+ \longrightarrow RC_6H_4O\text{-}CH_2CHOHCH_3$$

substantiated by the fact that 100% yields of sodium chloride were obtained after a few minutes when the appropriate sodium phenolate and propylene monochlorohydrin were mixed, whereas the yield of the desired ether after ½ hour was only in the range of 10-20% but increased to 84% after overnight refluxing when an efficient reflux condenser was used. The instability of the p-trifluoromethylphenol in basic solution and its general reactivity prevented the successful preparation of the corresponding <u>para</u> derivative.

The substituted-2-propanol was converted to the corresponding chloride without difficulty by the method of Liebermann[68] using thionyl chloride and pyridine. The yield of the chloride in compounds which possess <u>meta</u> substituents, was lower than those possessing <u>ortho</u> and <u>para</u> substituents, as was noted by Liebermann. No explanation for this phenomenon is offered.

The secondary ethanolamine derivatives were prepared in good yield by treatment of the chloride with ethanolamine overnight at 150°. Temperatures below 100° failed to yield any product. In comparison, the tertiary amines were prepared by overnight refluxing of a mixture of benzyl chloride, absolute alcohol, the secondary ethanolamines and potassium carbonate. The purification of these amines was finally accomplished by the removal of the unreacted secondary amine by formation of its ether-soluble nitroso derivative with cold nitrous acid. The desired product, the β-chloroethylamines, were obtained in good yield as their hydrochlorides by treatment of the tertiary ethanolamines with thionyl chloride and subsequent purification by recrystallization from absolute alcohol.

V. PHARMACOLOGICAL TESTING

Preliminary data concerning pharmacological behavior and paralyzing doses of the fluorine-containing α- and α-γ substituted glycerol ethers was obtained* according to the method of Berger[23]. These fluorine-containing central depressants appeared comparable in paralyzing action to the corresponding chlorine and bromine analogs, but slightly less effective than Myanesin. The _ortho_-fluoro analog was the most effective of this group. The strong _meta_-directing trifluoromethyl analogs were extremely effective, especially when the trifluoromethyl group was in the _meta_ position. The α-γ-disubstituted glycerol ethers possessed insignificant paralyzing action.

Preliminary experiments on the toxicity of fluorine-substituted 3-phenoxypropan-1,2-diols were conducted, using white mice. At paralyzing dose levels there was no evidence of gross pathology at the end of two hours. The manifestation of hemorrhagic kidney and marked liver discoloration was noted at the end of twenty-four hours. Hemoglobinuria was induced with large doses of the trifluoromethyl derivatives.

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* Appreciation is extended to J. H. Fellman for the pharmacological data.

In general, fluorine substitution did not increase the toxicity of the substituted 3-phenoxypropan-1,2-diols above that of the corresponding chloro- or bromo- derivatives.

α-and α-γ-Substituted Glycerol Ethers

Paralyzing Doses

$$R^1 - O - CH_2CHOHCH_2 - O - R^2$$

R^1	R^2	P.D.(a) mM/kg.	
2- fluorophenyl	H	1.9	0.2
3- fluorophenyl	H	8.0	0.4
4- fluorophenyl	H	2.8	0.2
2- trifluoromethylphenyl	H	2.0	0.2
3- trifluoromethylphenyl	H	1.5	0.2
2- fluorophenyl	2- fluorophenyl	10.0	0.5(b)
3- fluorophenyl	3- fluorophenyl	-	-
4- fluorophenyl	4- fluorophenyl	-	-
3- trifluoromethylphenyl	3- trifluoromethylphenyl	-	-

(a) The loss of the righting reflux in white mice for at least one minute was considered as criterion for paralyzing action. In all cases the use of 10% propylene glycol solution was employed as the vehicle for injection. The volume injected was never more than 0.5 ml. by subcutaneous adminstration.

(b) Intraperitoneal injection.

The fluorine-substituted N-(β-phenoxyisopropyl)-N-benzyl-β-chloroethylamine hydrochlorides will be tested in the near future for their effectiveness as sympatholytic agents, as demonstrated by their ability to block the pressor effect of epinephrine when administered intravenously.

VI. SUMMARY

It was demonstrated that the Williamson reaction is applicable to fluoro- and trifluoromethylphenols and such halogen compounds as glycerol-α-monochlorohydrin, glycerol-α-γ-dichlorohydrin, and propylene-α-monochlorohydrin. The mechanism of these reactions has been established to be the formation of sodium chloride and an epoxide by the initial loss of hydrogen chloride from the halide, and the subsequent reaction of the epoxide with the phenolate ion to yield the secondary alcohol-ether.

Fluoro and trifluoromethyl analogs of α- and α-γ-substituted glycerol ethers were successfully prepared, their effectiveness as central depressant agents undertaken, and the results reported. The ortho- fluoro and meta-trifluoromethyl derivatives compare favorably with "Myanesin" and will be more thoroughly investigated.

Fluoro and trifluoromethyl substituted N-(β-phenoxyisopropyl)-N-benzyl-β-chloroethylamine hydrochloride were successfully prepared and their effectiveness as sympatholytic agents will be determined in the near future.

The synthesis of the following new compounds is reported:

3-(2-fluorophenoxy)propan-1,2-diol
3-(3-fluorophenoxy)propan-1,2-diol
3-(4-fluorophenoxy)propan-1,2-diol
3-(2-trifluoromethylphenoxy)propan-1,2-diol
3-(3-trifluoromethylphenoxy)propan-1,2-diol
1,3-di-(2-fluorophenoxy)-2-propanol
1,3-di-(3-fluorophenoxy)-2-propanol
1,3-di-(4-fluorophenoxy)-2-propanol
1,3-di-(3-trifluoromethylphenoxy)-2-propanol
1-(2-fluorophenoxy)-2-propanol
1-(3-fluorophenoxy)-2-propanol
1-(4-fluorophenoxy)-2-propanol
1-(2-trifluoromethylphenoxy)-2-propanol
1-(3-trifluoromethylphenoxy)-2-propanol
1-(2-fluorophenoxy)-2-chloropropane
1-(3-fluorophenoxy)-2-chloropropane
1-(4-fluorophenoxy)-2-chloropropane
1-(2-trifluoromethylphenoxy)-2-chloropropane
1-(3-trifluoromethylphenoxy)-2-chloropropane

N-[β-(2-fluorophenoxy)-isopropyl]-ethanolamine

N-[β-(3-fluorophenoxy)-isopropyl]-ethanolamine

N-[β-(4-fluorophenoxy)-isopropyl]-ethanolamine

N-[β-(2-trifluoromethylphenoxy)-isopropyl]-ethanolamine

N-[β-(3-trifluoromethylphenoxy)-isopropyl]-ethanolamine

N-(β-phenoxyisopropyl)-ethanolamine

N-[β-(2-fluorophenoxy)-isopropyl]-N-benzylethanolamine

N-[β-(3-fluorophenoxy)-isopropyl]-N-benzylethanolamine

N-[β-(4-fluorophenoxy)-isopropyl]-N-benzylethanolamine

N-[β-(2-trifluoromethylphenoxy)-isopropyl]-N-benzylethanolamine

N-[β-(3-trifluoromethylphenoxy)-isopropyl]-N-benzylethanolamine

N-(β-phenoxyisopropyl)-N-benzylethanolamine

N-[β-(2-fluorophenoxy)-isopropyl]-N-benzyl-β-chloroethylamine hydrochloride

N-[β-(3-fluorophenoxy)-isopropyl]-N-benzyl-β-chloroethylamine hydrochloride

N-[β-(4-fluorophenoxy)-isopropyl]-N-benzyl-β-chloroethylamine hydrochloride

N-[β-(2-trifluoromethylphenoxy)-isopropyl]-N-benzyl-β-chloroethylamine hydrochloride

N-[β-(3-trifluoromethylphenoxy)-isopropyl]-N-benzyl-β-chloroethylamine hydrochloride

N-(β-phenoxyisopropyl)-N-benzyl-β-chloroethylamine hydrochloride

The preparation of fluoro isosteres of the essential amino acids and of the vitamins pyridoxine and pantothenic acid was unsuccessful. Only the corresponding unsaturated compounds, resulting from the elimination of hydrogen fluoride from the resulting monofluorides, or tarry materials were obtained.

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